MODERN TRENDS

IN

DERMATOLOGY

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MODERN TRENDS
IN
DERMATOLOGY

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INTRODUCTION

The task of the editor of any volume of the Modern Trends Series is not free from difficulty despite the assistance which he receives from his contributors and from those other colleagues who patiently answer his inquiries. His difficulties commence at the outset, for it is not an easy task to ascertain the principal modern trends in his subject, and so to plan the book that the majority of them receive attention further if the book is not to be a hotchpotch of disconnected chapters, the trends must be integrated so that the transition from one chapter to another is not too abrupt.

Obviously it is impossible to estimate the opinions held at home and abroad, so that every modern inclination in dermatology is discussed in fact, if this was done the book would be an encyclopaedia and not the work that it purports to be. A middle course has had to be steered, and the editor hopes that in making his decisions concerning the subjects which should be included he has constructed a book which will be of value both to dermatologists and to senior students of dermatology

The plan which has been pursued has been based on what is believed to be one of the most important trends of our times that is, the trend whereby the clinician, whilst keeping abreast of advances in his own province, endeavours to assimilate the knowledge relating to dermatology which is obtained by the investigations made by workers in other branches of science and medicine, and to apply these new discoveries for the benefit of his patients. Therefore, in this book there are many chapters written by men whose interests are not primarily dermatological, as well as chapters written by authorities in our own speciality

It has been suggested that it is a mistake to ask an authority in a collateral branch of medicine to write for dermatologists, for the authority may fail to appreciate the matters which are particularly of interest to the skin specialist and concentrate on matters which are of relatively little importance. This criticism may sometimes be valid, but those who make it fail to appreciate the important fact that a specialist in a collateral branch of medicine writing on his own subject, can assess the value of recent advances in his subject in a manner which few dermatologists can do For example, most of us have studied recent work on nutrition many of the observations made by experts in this science have not tallied with our clinical experience and we have been undecided as to the merits or demerits of the theories which have been propounded, and have not understood why statements put forward by reputable observers have failed to stand the test of clinical application. Professor Marrack's chapter in this book is illuminating as an expert in his own subject he can indicate where certain matters which have puzzled us have been criticized by nutritionists themselves, and we are left to draw our own conclusions as to the matters which we can accept and those which seem to demand further investigation.

INTRODUCTION

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The chapters on dermatological subjects contributed by those who are not dermatologists are leavened by chapters furnished by specialists in diseases of the skin. When deciding the subjects which the latter should be asked to consider preference has been given to a subject of wide scope rather than to one which—though important—is of limited interest. This has increased the difficulties of the authors, for it is not very difficult for a specialist to submit a competent monograph on a single subject, but in a limited space, to deal with such subjects as Modern Trends in Therapy or Endocrinology or Tropical Diseases is to undertake a formidable task. It is hoped, however that this strategy will increase the interest of the book for the average reader

Two of the most important of modern trends are those concerning the prevention of skin diseases and the rehabilitation of those who have suffered from these maladies. From the purely dermatological standpoint little has been done concerning the first of these matters Various activities in the spheres of preventive medicine, public health, general education and socionomics have influenced the morbidity of skin diseases thus, in Great Britain, there appears to have been a *reduction in the incidence of cutaneous tuberculosis which some associate with the* increasing interest taken by the authorities in the provision of uncontaminated milk. General education and the trends of fashion have done more than we realize to prevent the spread of certain infective dermatoses, but the field for basic investigation of this subject is open for pioneer investigation. As a result of data accumulated during World War II much is known of the incidence of infestations among certain sections of our population but a preliminary statistical social *survey followed by limited surveys concerning morbidity rates of prevalent* maladies in various population groups, would yield basic data which integrated with our knowledge of the aetiology of those diseases, might help us in the task of preventing skin disease One foresees that in future years when an important item in preventive medicine has been discovered, there will follow the dissemination of that knowledge among the population as a whole by the press, the cinema, and other vehicles of popular education

All of us pay lip-service to the adage that prevention is better than cure, but most regard the prospects of preventing skin diseases as so remote, and the problems of curing the sick so pressing, that we feel that such a long-term matter is not of immediate interest yet the reader is asked carefully to consider the point, and not to dismiss it lightly As the golfer adds impetus to his drive by a clean follow through so when we discuss aetiology and the anatomical physiological, biochemical, and psychological factors which contribute to the production of disease, we should always add impetus to our reflections *by projecting our* thoughts over the bunkers of our present difficulties and down the long fairway to the bourne which is our true objective.

Rehabilitation—or re-ablement—is a matter which has been seriously considered only recently The subject is integrated with aetiology and bristles with difficulties which await conquest. The ultimate solution for many cases oppressed with economic fears and burdened with psychiatric loads would seem to be the creation of industrial villages where each patient could live a sheltered *life within the* limits set by his disability and yet contribute his quota to the corporate life of the

community This has been done for the tuberculous, but, so far as skin patients are concerned, one of the major difficulties which can be foreseen is the problem of morale without keenness on the part of the inhabitants, the colony is doomed to failure. It seems probable that when dealing with tuberculous persons, organizers can exploit the factor of good morale, which in this case is perhaps an offshoot of *spes phthisica*. The morale of a man or woman suffering from a chronic cutaneous malady is probably as low in civilian life as it was in the Army and to organize successful industrial colonies for such persons would seem to be a more difficult proposition. But because the proposition is difficult, that is no reason why it should not be attempted on an experimental scale.

The discussion of these problems leads one to make several reflections first, one notes that team-work is a modern trend which is becoming more prevalent and that nowadays few important papers are the work of a single author In the wider spheres of investigation, team-work is essential, and scientists, statisticians, and medical men contribute their quota to an investigation. Difficulties sometimes arise because the individuals of a team do not appreciate each other's points of view and methods of approach further the planning of an investigation may be jeopardized because those concerned do not appreciate the assistance which they may receive from a statistician.

Secondly the *raison d'être* of the clinician is to relieve human suffering. Concentration on rare diseases has led many postgraduate students to believe that the study of these rarities is more important than the study of the more common maladies and yet seborrhoeic dermatitis, psoriasis and the group of diseases which may be loosely referred to as the infective dermatoses have throughout the ages caused more human suffering than all the dermatological rarities combined. Yet our knowledge of the aetiology of psoriasis and seborrhoeic dermatitis is small and our beliefs concerning the aetiology of some of the infective dermatoses are matters for controversy The more senior dermatologists recognize that investigation of these matters is of urgent importance, but many of the junior men do not appreciate this fact. I have advised several of the latter to write an M D thesis on impetigo contagiosa, for the clinical material is plentiful, and the work is difficult and important. These men, however have looked at their mentor pityingly and have passed on. *Perhaps they were right* but a good thesis on this subject is likely to be of more value to humanity than one based on a study of an insignificant number of cases of acute disseminated lupus erythematosus or hereditary bullous epidermolysis.

Thirdly Professor Stokes and Dr Beerman have something to say of the shackles of The Practice they might also have referred to the shackles of the Clinic, for in Great Britain and elsewhere many dermatologists capable of original creative work are loaded with a burden of academic and clinical responsibility in hospital which, added to the demands of their practices, leaves them scant time and little energy to do the pioneer work of which they are capable. Further they have not the leisure which is necessary for the slow but arduous evolution of ideas. The emancipation of the dermatologist, so that he can work on the prevention of skin diseases, the rehabilitation of the disabled, the application of statistical methods, the study of genetics and other matters, is a trend which, because of economic

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pressure and other factors, we appreciate but dimly Yet this emancipation will come, provided we retain our civilization and our way of life. The genesis will have been in our generation although it will probably be our successors who will pursue these courses

It is with these and with other considerations in mind that this book has been planned and the reader is asked to remember that the purpose of the book is as stated in its title Although many recent advances in dermatology are discussed, it is their influence on the trend of dermatological thought which is of paramount importance and has necessitated their inclusion in the book

My final and most pleasing task is to offer my thanks to all those who have devoted their time and labour to the preparation of the chapters to Lord Horder —the General Editor of the series—for his advice and encouragement, to Dr A. Garland—the Medical Publishing Editor—Mr W R. Lloyd—the Medical Publishing Manager—and their staffs, who have nullified many of my editorial omissions by the efficiency of their sub-editing.

R. M B MacKenna.

CHAPTER 1

THE DERMATOLOGY OF YESTERDAY TO DAY AND TO MORROW

By John H. Stokes and Herman Beerman

The dermatologist has sustained a post-war stimulus. A liberal dose of the percentage elixir compounded of the proportion of cases of dermatology to those of all other diseases in the armed Forces, has liberally advanced his self esteem. On this exhilaration he might ride for another quarter of a century But the realities bear a somewhat different interpretation upon which we shall risk emphasis in an opening chapter on *Modern Trends*. Bluebeard's wife, it will be recalled, as she knelt beneath the suspended scimitar cried again and again to her sister in the watch-tower Sister Anne Sister Anne, do you see anybody coming? The reply monotonously described the empty road. But with the last cry a small cloud of dust appeared on the horizon and grew rapidly The situation was saved by the arrival on the scene of a corps of young investigators headed by the victim's brother

Dermatology has repeated the evolutionary history of medical specialties. Hebra, assigned to pick skin cases from the patients of a chest clinic, proceeded in thoroughly orthodox fashion to develop a bud from the parent trunk of medicine. The first step is the invention of a nomenclature and the application of the objective descriptive discipline to the material. A group of word-pictures with labels attached is then subjected to what without invidious implication one may call the most primitive type of analysis, the anatomical and, under the microscope, the histological or histopathological study The application of fixed tissue pathological interpretation greatly advances the breadth and depth of the special discipline, but it has its limitations, which become especially apparent when the selection of methods is limited (as to haematoxylin and eosin for example) and the viewpoint is photographic rather than physiological or functional. It is possible for a specialty never to progress beyond the descriptive point in the individual mind, and the hewing of wood and drawing of water represented by the standard case report to go on indefinitely without regard for the possibilities of reafforestation, arboriculture or irrigation. Such a situation would be an entanglement with descriptive pathology and pathological anatomy We, as individuals and specialists, can afford, by a perusal of the journal indices of fifty years, to ask ourselves to what extent we have been thus entangled.

But happily as we have ventured to intimate elsewhere (Stokes and Beerman, 1937 1942) the morphological era has been succeeded by a functional one, still in its beginnings but already responsible for great advances. Basic normal physiology caught up with morphology and on its foundations climbed to immensely significant heights in the work of Lombard (1911 1912) Krogh (1930) and Lewis (1927) on the behaviour of the cutaneous vascular system of Eppinger (1913),

pressure and other factors, we appreciate but dimly Yet this emancipation will come, provided we retain our civilization and our way of life. The genesis will have been in our generation although it will probably be our successors who will pursue these courses.

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accomplishments of Sabouraud (1894 1910) in descriptive mycology but we are kicked into activity and excitement by the identification, analysis, and demonstration of the relationship of primula toxin and trichophytin to the problems of allergization by Bloch and his colleagues (1926 1934).

Metabolism both of the skin itself and of the body as a whole in relation to it, has made substantial advances, some of which are developing clinical applications of considerable importance but much undisclosed territory awaits exploration Two sentences from a recent review by Calvery Draize, and Laug (1946) emphasize the relation between viewpoint and progress

> A search of the literature has revealed that in most instances the skin has been regarded as a membrane whose viability was not necessarily concerned with the passage of substances inward. Greater stress has been placed on the mechanical and chemical properties of the skin, and it is therefore not surprising that the relationship between livingness and permeability has received scant attention.

Searching, and suggestive for the future, though this remark is, it does not minimize the significance of work such as that of Folin Trimble, and Newman (1927), who devised and applied a method Urbach and Lentz (1945) and their associates, and Trimble and Carey (1931), Tsukada (1933), Pillsbury (1931) Pillsbury and Kulchar (1934 1935), Pillsbury and Sternberg (1937), Sellei and Spera (1938) and Cornbleet (1940), who have painstakingly elaborated our still far too scanty knowledge of carbohydrate in the content and function of the skin and the influence of diet upon it. The studies of Koeppenhoefer (1936) covered the analytical chemistry of the skin with reference to lipoids Wile, Eckstein, and Curtis (1929), for example, applied the lipoid chemistry to the understanding of lipoid carbohydrate relationships in diet, via the xanthomas and Stevens (1935 1936) from another angle invoked the decomposition of lipoids in the skin to form peroxides to explain the anti-infective and parasiticidal action of ultra-violet light. In the field of water metabolism similar bridgings have occurred. Schiff (1929), for example pointed out that, even though the experimental animal dies of the toxic effects, the usual signs of inflammatory reaction to infection are absent if the water-content of tissues is inadequate. Földes (1933) noted that protein was essential to such effects, and that on a diet which is rich in carbohydrate it is impossible sufficiently to dehydrate the skin to produce an inhibition of inflammatory reaction. This linkage of carbohydrate metabolism and inflammatory reaction in the skin was amplified in developing a concept of dehydration as a means of controlling inflammation, by Kulchar and Alderson's observation (1936) of the effect of water starvation on lethal pyogenic infection in rabbits Then, from another angle illustrative of the twig-like and branch-like ramification of knowledge into unexpected territory the missing link suspected by Pillsbury and Kulchar (1934), when they failed to parallel the glucose and water content of the skin, turned out to be in all probability lactic acid produced from carbohydrate, the vasodilator intermediate factor in the skin inflammation picture this theory was fully elaborated independently by Menkin and his associates (1931 1934 1936) when studying pleural inflammation The lactic acid factor by its effect on the pH of the exudate largely influences the cellular content of that exudate and the formation of pus.

Dale (1929 1934) Lewis (1927) Grant *et al* (1936) Brown (1932, 1936), and Isaac Starr (1928 1930) on acetylcholine and histamine of Schiefferdecker (1921 1922) Kuno (1934) Marchionini (1934 1938) and the more recent experimenters, Burckhardt (1935) Usher (1941) Cornbleet (1935) Peck and his co-workers (1938, 1939) on the sweat mechanisms of Unna and Golodetz (1910) and Unna (1913 1928) Pautrier (1928) and Bloch (1927 1928) on microchemistry of Bazett (1938) on skin temperature of Eppinger and Hess (1915) Brill (1926) Szondi (1927), Brack (1935) Goldsmith (1934 1936 1939) Rogerson (1934) Rogerson and his co-workers (1935) and Strauss (1935) on the clinical side of neuro-dermatology and of Lewis (1927) Mittelman and Wolff (1939 1942) Rothman and his co-workers (1929) Leriche and his associates (1933 1937) on skin neuro-physiology In the attempt to select names one encounters at once the two types of investigative progress to be mentioned later—(1) the single isolated brilliant contribution and (2) the consistent development of a field of investigation.

Static pathology has been amplified by pathological physiology or functional pathology in the extended work on the lipoidoses of the skin by Urbach (1938) Thannhauser (1940) Thannhauser and Schmidt (1946) Weidman (1941) and Montgomery and Osterberg (1938) At this point the gradient of advance decreases and in the fields of water balance, glucose, porphyrins, vitamins we find ourselves on a thin front with investigators and massive contributions fewer and farther between these are, of course, the new domains of chemical physiology Then as we turn to the older immunological salient, we enter upon the golden age of pre-war achievement the study of the allergic state epidermal systemic, infection-allergic, in which the flock of good not to say great, names becomes so large that citation beyond the nomination of an olympian or two such as Jadassohn Bloch or Coca becomes a supererogation, and invites for the unfortunate discussor a stoning by the friends of the omitted (Stokes, Beerman, and Ingraham 1938) In the area of bacteriology—to use a schoolmaster s term—great humps and painful hollows still abound or to shift the metaphor our knowledge is as full of holes as Swiss cheese. In fact, if knowledge of the basic facts or norms is a test we hardly know that we are dealing with cheese at all so huge is the proportion of holes in our understanding of the bacteriology of the normal and of the abnormal skin. The behaviour of saprophytes and pathogens, the mutations and pleomorphism of organisms, the shifts that there is reason to suspect occur from one to the other under the influence not of the organisms evolutionary drive, but of the host s responses and initial status, are still largely unexplored. Americans have been deeply impressed with studies such as those of Price (1938) which Pillsbury *et al* (1942) has been following through. Burtenshaw (1938 1942, 1945) has materially advanced our knowledge of the factors involved in the self-disinfection of the skin. Burky (1934) and Hopkins and Burky (1944) initiated a series of conceptions which we have been slow in following up but which are finding expression in the recent paper by Boe (1946) on the development of staphylococcus bacterial allergy Norrlind s (1946) monograph on the influence of respiratory infections on the course of Besnier s prurigo is another example of a trend In directions such as these, the fluid, the functional behaviouristic slant is replacing the elaborately descriptive static quality of earlier work in a critically important field of advances in dermatology We, of course, bow at once to the monumental

accomplishments of Sabouraud (1894 1910) in descriptive mycology but we are kicked into activity and excitement by the identification, analysis, and demonstration of the relationship of primula toxin and trichophytin to the problems of allergization by Bloch and his colleagues (1926, 1934).

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We mention these studies and sequences, which we have reviewed more fully elsewhere (Stokes, Beerman and Ingraham, 1938) not so much for their worth as landmarks and their specific implications and applications, as for their value as examples of the *modus operandi* of the advance of functional knowledge of the skin—and not of the skin alone, but of the skin in relation to the body and to the sum total of physiological (and as we shall say presently psychological) processes.

REFLECTIONS ON THE MECHANISM OF RESEARCH AND ADVANCE IN DERMATOLOGY

We have thus incompletely sketched some high points in the development of dermatology from a label and picture specialty to the beginnings of a true functional discipline, capable of meeting on equal terms the best that clinical *medicine has to offer with intent to examine the trends and processes for principles* applicable to the human performance of its votaries. Speaking *en famille* we must concede that too little of the work has been done by dermatologists, though undoubtedly vitally important have been some of their individual contributions. In a remarkably revealing fashion a dermatologist of our acquaintance once gave away the secret of such non-participation in a letter full of questions about how to do this and that You know he said in effect we men in practice just haven t *time to look into the reasons for things We just turn to you fellows (investi* gators) for the methods, and then we apply them A better picture of *spongiosis dermatologica* was never put into words

As Gans (personal communication) said again in effect, after the grand tour of a national dermatological field You gentlemen are devoured by your practices. There are too few of you and the standard of living is too high There are so many dermatologists that no more than a bare living will ever be possible to most of them Few or none will have establishments, none will be tempted to tour the scenery of their country on rubber tires Instead they will have to turn to the more austere joys of the intellectual life. It is they who will advance thought and knowledge through research undertaken for love, and the wise exploitation of leisure

We shall say no more about the rubber-tired sponge, the week-ender the man who must have his eight hours sleep, the dermatologist who sees 100–200 patients a day (*sic*) and the author of the gelled or static case-report, number 26 in the literature series, and turn to the serious business of methodology the foundation of functional advance. The first step in the opening of a field of authentic functional investigation is the devising of a method or an apparatus, though we willingly concede the usefulness of finding an already existing method buried in the literature, and of applying it This calls for an originality and imagination that many do not possess, but more persons have these gifts than is commonly recognized their hesitancy in stepping off comes from (1) fogginess in outlining the problem they wish to attack (2) a feeling that they must find out all about what everyone else has done or thought before making a beginning (so-called reading the literature) (3) a feeling that by the time they get anywhere someone else will have arrived before them largely because the competitor has access to greater facilities and support. We leave out of account (4) the laziness

that besets us all, the shying away from the dismal drudgery that is part and parcel of every significant research as of every worth-while achievement. Like kittens, we must all have our faces held to the saucer and be choked before we begin to eat

For creative work we must have more *incentive*, more men applying, more confidence among all of us that each or any of us may be found to carry the vital spark. We must have protocol and methods. Further we must have guidance Research in the calcium field has for a long time been blocked by unsatisfactory methods of determination, in which the margin of error is about equal to the differences in behaviour observed. Did we think this out for ourselves? No, we had to go to a physiological chemist of the highest rank to get perspective on it. There is constantly available, and too little used, a vast amount of perspective giving insight into the worth of problems and methods, which in our experience is always most generously shared by the basic scientist with the informed amateur or clinician who has an idea. Similarly there is an equal amount of technical helpfulness available provided the recipient of it proves to have, or can be vouched for as having, seriousness of purpose, persistence and time Guidance is *therefore*, available for almost any reasonable project, once it is adequately outlined or protocolled. We would remark again here on the common confusion that exists between guidance and facilities and particularly we wish to emphasize that organization and equipment, while often precious and time-saving, is far less essential than is commonly conceived. Research is done with the mind rather than with glass, metal, reagents, bricks, and mortar One has to see the stark simplicity of the late Sir Thomas Lewis's laboratory to realize how true this is. What, we cry one of the greatest physiologists skin physiologists, of his time and not a kymograph or a needle and diaphragm in sight?

After spending odd hours during a summer compounding paints for a celluloid strip skin-colour comparator like Sir Thomas's, we began, stop-watch in hand, to put down on paper the time-colour-posture relationships of flushing and paling of the hands and feet, feeling that we might be on the way to a simple measure of vascular tone in appraising the stasis *factor in the dermatoses of the hands and feet*, comparable in possibilities for clinical use with complex and expensive equipment such as the Macbeth illuminometer or the Sheard photo-electric equipment Routine demands, administration, and practice buried the study but it left behind it, as did other similar experiences, the indelible belief that dermatology dealing with the most accessible of the great structural groups of the body is still in the Benjamin Franklin kite and-key stage of research potentialities. What is needed is less laboratories and equipment and more interest in the particular go the reason for things, on the part of dermatologists, and the guts the personal sense of responsibility for seeing work through and finding out why not in the field of the rare and occasional case, but in the field of *the commonplace* and even the normal.

It would be foolish to deny that some selection for brains and training for such a programme of dermatological advance would be worth while. Our post-graduate centres and our specialties qualification boards and professional societies should be looking into this, instead of focusing too closely on fitness for the commonplaces of practice— Practice who is too often a disreputable old harridan flaunting the

tarnished sequins of an utterly irrational and soon to be out moded therapeutic dress. When one recalls that to the greatest training centre of the past quarter of a century nobody was admitted who had less than the preliminary seal of a recognized institute of pathology one wonders whether it is not the positive duty of great university centres, for example to exclude the predestined hack from their staffs by every device, and to open the gate to advanced training only to those who can show with evidence of the creative gift and the analytic mind more than ordinary equipment in a special discipline such as physiology bio-chemistry bacteriology and mycology not to mention metabolism allergy (though goodness knows that field too needs overhauling as does also neuro-psychiatry)

We have remarked as a mode of advance, on the single brilliant study by someone not again heard from in our field, and have contrasted this with the determined pursuit through years of a line of basic investigation Two needs seem immediately apparent. The first is to unearth the often buried single gifted contribution (or one reasonably suspected of being such), whether of fact or method by bibliographic research and to set it to work after confirmation and the second is to build up preferably in institutions or organizations rather than on the foundation or keystone of a single mortal brain, a consistent effort, equipment, and tradition for following through an interrelated group of problems. The name of Emil Fischer in the chemistry of sugars and of Jadassohn Bloch or Sir Thomas Lewis, will recall aspects of our meaning. Of the former need it may be said that no new approach should go for years unchecked and unconfirmed or rejected, as now it too often does. There are enough methodological instruments lying about unused in the vascular sweat (Buley 1938) glucose metabolism (Urbach and Lentz, 1945) and bacteriological fields (Pillsbury *et al* 1942) some of them, if verifiable, quite equal to turning current practice upside-down to keep us busy for a generation without a single wholly new improvisation Of the second need the inspiring and yet tragic comment is inescapable that, as Krogh (1939) has said our warfare against the unknown is still of the guerrilla type that individual men of stature besiege and subdue the Unknown With their going, when they head schools or laboratories something fails. No matter how perfected the organization centring around them may be it cannot make research It can merely assist it. Its vitality lies in the tradition of research-minded disciples to whom it gave shelter and inspiration Too often over-organization defeats this function burying it in a mausoleum of brick marble, administration and regimentation

One can say gladly that, as in the recent triumphant synthesis of penicillin, a happy function of this latest war has been to show how vital is the going back and forth of a sniffing, constructively minded group of men over a field occupied by dozens of investigating groups, each making signal individual contributions But we need not ask you who brought the penicillins to the light of day

The deflecting alliances

It has seemed to us that dermatology is faced with another problem in addition to that of its rejuvenation through more and better research—that of partnerships and alliances. Quite early in its career the specialty was deflected, shall we say into a liaison with venereology and particularly with syphilology Great was the gestative outcome of that alliance, we must admit but the base on which it rested

i.e. the cutaneous manifestations of syphilis, was *too* incidental and superficial to last. Syphilology performed a service for dermatologists in that it tempted, at times even inspired, them to look below the surface at Medicine and its basic sciences for rounding out and explanation. But now dermatology as we are trying to conceive it as a medical specialty is strong enough and has domain enough of its own for independence. *It is hazardous to prophesy since prophets are nearly always wrong* but it seems to us that the drift of venereology especially in the coming antibiotic era, will be away from dermatologists, who can now hardly find the lesions on which to lecture, and toward the field of public health. The present failure of treatment to reduce the incidence of venereal disease seems to us to mean that comparatively *new* and *often even* non-medical approaches will be necessary for venereal disease control. Eventually venereology will have so radically different a content and outlook from dermatology that the alliance will break up in incompatibility and perhaps the sooner the better

Other alliances, more or less inescapable, and indeed very useful in their day have been those of empiricist therapeutic ritual salves, baths, and radiotherapeutic bombardments among many which operate on the principle that, the skin being a surface structure it must be dealt with by surface methods. Conspicuous, for example has been the failure under this principle to control the action of topical medicaments by a study of the action of their vehicles. It is by no means inconceivable that the elaborate traditional prescriptions are resolvable, so far as major activity goes, into the protective effect of unadulterated grease against contact allergens *and the penetration of infectious agents into alterations of pH and* alkali neutralizing power into vasoconstriction, direct and reflex and into psychotherapeusis, usually applied unawares by the operator One has only to watch *the recovery under dehydration and anti-glucogenic therapy alone of* extensive pyodermias, and the variety of medicaments which cure the psychoneurosis of the rosacea complex, to laugh at the unexamined therapeutic empiricism of the prescription writer

One must bow and one should smile too at the alliance with mechanotherapy *that has reached its peak and seems now on the decline*. In some fields x ray and similar irradiation techniques, for example, still remain supreme, as in the malignancies, because there is nothing better to offer (cf., however Amersbach *et al* (1946) on organ extracts). But too often we are now called upon to realize their purely symptomatic quality and their damaging and dangerous effects. While we have been using them we have given comparatively small thought to their *modus operandi*, and to the extent to which their effects have been due to influence upon deeper structures (e.g. the endocrine glands and the nervous system), and again, to suggestion itself

Three examples of specific fields for investigation and creative thought

The foregoing animadversions have no other purpose than to help persuade the dermatologists of the coming generation to question always *QUESTION EVERYTHING* and to try for a method of finding out something, about something, about which they have been wondering. We pass now to a somewhat more detailed exemplification of this point of view in the fields of two or three functional problems in which we have been specially interested These are the mechanisms

controlling the course of cutaneous infections particularly the *flush mechanism* (vascular) the *virus pyogen sensitization sequence* other aspects of *infection symbiosis superposition induced allergy* and *allergic interplay* also certain *psychosomatic trends* We are not offering the results of systematic research but attempting a stimulative and imaginative commentary

The flush mechanism—A fascinating field of study close to the surface and generally neglected by dermatologists, is the colour play of the skin as we call it the vasodilatational and vasoconstrictor reactions. Though specially concerned with the flush we recognize that vasoconstriction at certain levels, by changing the proportion of blue venous blood in circulation produces a cold lividity that is not true arterial flush instead of the anticipated pallor Whilst not completely separable the come-and go play of colour and a persistent congestion can be distinguished, the former an expression of unstable factors, the latter perhaps, of more deep-seated functional warps The fluctuation of colour serves the clinician as an indicator mechanism pointing to the tension elements in a situation. When it adds itself to a persistent flush as on the hand, foot, or face, it can give rise to acute localized congestion which might be called stigmatization (We borrow this term from its conventional use in the literature (Klauder 1938) to express vasodilatation regional or localized induced by psychic tension) Thus the mere inspection of a dermatitic hand leads to a distinct darkening of the red colour In one patient with a dermatitic and ecthymatous leg, we were able repeatedly to demonstrate to associates and students the intensification of the erythema and the turgor of the superficial veins when her troubles were discussed with her A veteran of World War I who lost a leg, demonstrated his occult tension (for he was outwardly a calm person) by increased erythema and sweating of his eczematous stump when finally induced to drop his reticence and describe his experiences in the Argonne.

Physicians hands are notoriously demonstrative of vasomotor stigmatization We have known the concealment of hand dermatitic lesions, while leaving another site exposed in order to transfer the patient s attention to result in a vasomotor recovery that could hardly have been explained by the local concealing application We have observed the influence of resentment under parental domination to maintain the angry flush that prevented the clearing of an acne and with it the response that followed calling off the parents and letting the patient go his own way and disregard his skin We have seen an eczema—asthma—hay-fever (EAHF) patient whose mother had been the *bête noire* of his existence, flush repeatedly some 15 or 20 seconds after hearing the word mother his facial skin turned a dark angry red and there was exacerbation of itching the patient s eruption was limited almost entirely to the areas of flush. Frequently one finds resentment, equally with anxiety and insecurity at the bottom (apparently) of the heap in vasodilatational phenomena. From the recognition of the vasodilatation alone one progresses to the association of vasodilatation with the localization persistence and exacerbation of a considerable range of inflammatory processes, notably infections, seborrhoeic, mycotic, and pyogenic. Acne rosacea rosaceal seborrhoeic dermatitis, the French ear (streptomycotic otitis externa) staphylodermias of the scalp (including the nape localization of Vidal s lichen in the physiological naevus) all then begin to appear in the light of neurovascularly conditioned (though not

caused") dermatoses. They are influenced, often profoundly and especially as to exacerbation and chronicity by the flush mechanism.

What alls this page of statements, as one reads it? It is, of course, a series of *ipse dixit's*, dependent upon *our* eye *our* point of view and *our* interpretation. It is, as stated, devoid of measurable evidence, hence rateable as impressionism. It is unsupported by citation of parallels, or supportive facts on an experimental or observational basis, with plausible reasoning about mechanism and theories of the *modus operandi* Yet all these things already exist in embryo in the literature or can be supplied by experimental ingenuity

The first necessity for the systematic study of colour play in all its relations is a method of quick mensuration of which the patient will not be aware. In this the eye so far is unsurpassed unless perhaps, by the photo-electric cell concealed from the patient's view All the experimental studies of emotional responses in the skin that we have seen, such as the really remarkable work of Mittelman and Wolff (1942) and their associates, necessitated harnessing the patient to an apparatus and then subjecting him to experiment yet it has been shown that so simple a test instrument as the stomach tube (Mittelman and Wolff, 1942) requires an education before its findings can be trusted. Moreover the changes are often rapid and an instrument such as Sheard's (Sheard and Brunsting (1929) and Harris, Leddy and Sheard (1932)), at least as so far described, is too slow Hardy's (1939) has not so far been applied, to our knowledge. In any event, the challenge to devise a method is there. If Mittelman and Wolff, and again Usher (1941), could observe vasomotor changes in the gastric mucosa under emotion and the clearing of a gastritis simultaneously with its rosacea, we ought to be able to measure the colour-play of a dermatitis or an atopic eczema or neuro-dermatitis, also the vasomotor response to various forms of treatment.

On the score of suggestive physiological correlations for colour-play phenomena there exists, even in our limited reading, a variety of material for intriguing hypotheses on which experiment might be based. The histamine substances are the great vasodilators of the human chemical system. What are the possible sources of the histamine substances which may initiate and maintain a *vasodilatation* in the skin? The acetylcholine discharged at the termination of a motor nerve (Grant *et al* 1936) and the bacterial flora of the intestinal tract (Kendall *et al* 1926) occur to one at once. It is not inconceivable that muscular tenseness may maintain an excess of acetylcholine in the body despite enzymatic control. Watch the professor's hands suffuse and his face flush as he lectures, and speculate whence his body obtains the vasodilators involved in such a reaction perhaps in part they may come from increased intestinal peristalsis, which moves about the histamine-containing outer layers of his bowel contents for better absorption of histamine, and in part from the restrained muscular tenseness of the situation. Again, give a peristalsis-provoking enema to a face-flusher and watch him turn scarlet, or give a drastic cathartic to a patient with exfoliative dermatitis and watch him pale almost to normal in the next 24–48 hours. The former's histamine reservoir may be slopping over the latter's may have been emptied. The contributions of Harmer and Harris (1926) and of Williams (1938) on the distribution of the histamine erythema, as compared with that of erythematous inflammatory

lesions of the face neck, and flexures, seem to us very much in point. Elsewhere (Stokes and Beerman 1932 Beerman and Stokes, 1934) *in discussing the* rosacea complex, we have commented on the influence of disturbed gastric function in affecting the histamine-producing capacity *of the intestinal flora, and* have suggested that this mechanism may explain the physiological linkage between the *state of mind* and the flush

These reflections are here offered not as new conceptions of established worth but as humble samples of stimulative thinking, that seeks to combine the clinical observation with the known and investigable hinterland of physiology bacteriology and physiological chemistry They are a legitimate exercise of constructive dermatological imagination as long as they are used as stepping stones to processes of exact verification Upon them we may cross to a rational as distinguished from a hit-or miss therapeusis, *as in the use of hydrochloric acid by mouth for* paling the flush areas of the face

The field of *vasoconstriction* offers fewer but none-the-less interesting possibilities for speculation Since the work of Adson (1931) and of Leriche with others (1933 1937) on the role of the sympathetic nervous system in ischaemic types of disturbance a flock of correlations can easily be gathered together Vasoconstriction underlies causalgias and the skin manifestations associated with them There is even now a momentary passion for sympathetic ganglionic block in controlling infections of blue cold feet One may think of multiple morphoea, which we have seen associated with epidemics of poliomyelitis, as an expression of virus injury to the sympathetic nerves—and conceivably even to the efferent vasoconstrictors which accompany sensory nerves—associated perhaps, with a sort of sensory polio This is getting a bit wild we do confess but recall the association of hemiatrophy from Gasserian ganglionitis of virus origin (facial herpes zoster) and hemiatrophy associated with linear scleroderma in the same sensory nerve distribution We have one more wild shot to fire before leaving this subject s mangled *remains upon the arena sands and fleeing the scene.* Is it impossible that the common wart and the areate alopecic spot may have one thing in common—the extinction of the wart by a localized stigmatic and probably transient vasoconstriction and the appearance of the bald spot following a localized regional vasoconstriction that temporarily or permanently disturbs or extinguishes the function of the hair bulb? Without further comment, we pass to a similar *tour de force* in the field of infection mechanisms.

Some infection mechanisms—the virus pyogen sensitization sequence

For a number of years we have been concerned with the reasons why in a number of the inflammatory dermatoses, and particularly those in which pyogens play an exciting role, patients do not get lastingly well In other words, we have been concerned with the problem of infection relapse. (By pyogens are meant the groups of coccal bacteria, chiefly streptococci and staphylococci commonly responsible for leucocytic types of inflammatory reaction and for pus formation)

Among a variety of influences, conceivably contributory is that of the sensitization of the individual victim to one infection by another For as infection is now well known to broaden the base of all forms of allergy one infection may easily be conceived to broaden the base of susceptibility or allergic response to others.

In 1937 Stokes and Callaway reviewed this question in connexion with what we now call the "virus-pyogen sequence" in infection-allergic phenomena. "There are many reasons based upon observation of the course of various virus diseases, ranging from variola to influenza, for believing that a virus infection after a rather definite incubation or refractory period directly incites, probably by an allergic mechanism, a second wave of infective manifestations, streptococcal or staphylococcal in character." Such mechanisms probably play a part in the diseases discussed by Shope (1939) as "complex infections."

As additional illustrations of the point, Stokes and Cathcart (1923) as early as 1918 began to accumulate observations on the swing of arsenical exfoliative dermatitis toward pustular manifestations after upper respiratory infections; with Kulchar in 1934 attention was called to other aspects of the infection-allergic interplay in this "drug eruption," and it bids fair through the use of a Milian (1929) "biotropic" or infection-activation mechanism, to be of importance in explaining drug reaction to the sulphonamides and to penicillins. Infectious or catarrhal jaundice in the course of arsenotherapy (Stokes, Ruedemann, and Lemon, 1920), infectious diarrhoeas of probable virus origin with ensuing purulent otitis media (Keeler, 1920; Terrell and Owen, 1935; Jankelson and Massell, 1936), and, of course, influenza, notably in the 1918 epidemic, furnished innumerable instances of the virus-pyogen sequence in the onsets of staphylococcal and streptococcal pneumonia, purulent empyema, otitis media, and other pyogenic complications. In 1936, Stokes and Callaway (1937) were able to collect 134 cases of apparently direct relationship between pyogen flares in various dermatoses and virus infections of the naso-respiratory and gastro-intestinal type. They could even identify a latent or refractory period of 7–11 days in 60 per cent of cases, similar to that observed by Leipner (1935) in an outbreak of erythema multiforme in a boys' school. On the experimental side, the work of Glover (1941) with the influenza virus in ferrets is most suggestive; the role of streptococci in following through, so to speak, on a virus infection, and the necessity for the presence of both virus and pyogen for the production of clinical effects are implied. Stuart Harris (1945) insists that the sequence relationship of the virus and other types of infection including *Staphylococcus aureus*, has never had adequate consideration. In Stokes and Callaway's paper attention is called to the production of light sensitivity following virus infection, and in the ensuing remarks some ramifications of the problem are suggested. We quote: ". . . an interplay of factors which sometimes makes it difficult to distinguish cart from horse, marked the flares of previously light tolerant acnes following short sharp exposure to New Jersey (seashore) sunlight under conditions suggesting latent incubating or active intercurrent (virus) infection. . . . The relation between light as a sensitizer to pyococci, . . . pyococci as sensitizers to light and either or both as tied up with sensitization to metals such as nickel (nickel-pyogen sequence) (Cormia and Stewart, 1935) or to chemical compounds such as gold sodium thiosulphate and the arsphenamines, deserves further observation. . . . It affords interesting reflections on the suggestive type of thinking, that the course of one of our cases, plus Urbach's discussion (1938) of light sensitivity, has led us more and more toward the idea that the locus of the change which induces light sensitivity in many cases, is not an allergic reaction of the skin, but a virus-pyogen shift or sequence in the intestinal

flora this probably establishes a streptococcal or other bacterial preponderance after the virus infection that encourages the production and absorption of porphyrins, with their light sensitivity inducing effects The sequence is of interest, too in explaining exacerbations of pruritus ani with dermatitic perianal collarettes and with inguinal intertrigo Even catarrhal vulvovaginitis (*Micrococcus catarrhalis* infection) after naso-respiratory virus infections, can be included in a sequence of this sort The fungus-pyogen sequence, *to which* Darier Ravaut, *and their co-*workers (Darier 1928 Ramel 1929 Ravaut and his colleagues, 1930) devoted so much stimulating research (levurids, streptomycotic intertrigo and the Darier Ravaut Ramel *syndrome*) *is an infection-allergic sequence of similar type with* the widest significance as an explanation of the bacteriology of epidermophytons of the feet and groins and so-called ids fungal and bacterial

It has been exceedingly interesting to watch the growth of the conception of naso-respiratory incitement of exacerbations in Besnier s prurigo neuro-dermatitis and, to us the whole eczema—asthma—hay fever complex as illustrated in the recent papers of Norrlind (1946) and of Bøe (1946) These investigators emphasis seems to us to be primarily upon the study of infection allergy to what in our virus-pyogen-sequence ideas appear as secondary invaders, and upon the means of desen*sitization to them rather than to the primary sensitizing virus We too emphasize the* use of very small doses very slowly advanced, in our use of staphylococcus toxoid and bacterial antigen for what we call a hyposensitizing as distinguished from a bacteriological immunization technique But we are looking now towards a potent influenza virus vaccine for a preventive of the primary invasion by *virus* as an accessory or perhaps even a more fundamental approach to the virus-pyogen sensitization complex in these widespread affections.

Virus transmutations —This whole problem of virus pyogen sequences and primary and secondary invaders is shot through with another fascinatingly suggestive group of phenomena, thus far largely studied in the laboratory and insufficiently understood by dermatologists and others This is the transmutation of organisms from non-filterable to filterable forms under as yet not fully under stood but in part nutritional conditions Tyrode s medium was employed by Kendall (1926) in producing filterable from typical non filterable forms of typhoid bacilli, the ictero-haemorrhagic spirochaete and other visible pathogens with established identities. Rosenow (1944 a, b and c) has recently reported studies of a filterable infectious agent derived by various nutritional and cultural devices from pneumotropic streptococci which he reports as capable of reproducing in mice lesions identical with those produced by a known influenza virus. Jaquette Convey and Pillsbury (1946) review the literature of the Kaposi varicelliform eruption and report the presence of the virus of herpes simplex—vaccinia virus had of course, long been suggested These authors intimate that streptococci and staphylococci are an essential part of the picture. On the other side of the problem studies such as those of Rantz and his co-workers (1946) on epidemic naso-respiratory infection and streptococcal invasion, led them to the conclusion that the apparent increase of streptococcal complications after virus epidemics is fictitious and was due to the importation of streptococcal carriers into the personnel they studied. We have ourselves realized the complexity of this problem, but have thought that we saw reason to believe that there is a difference between virus

epidemics in the pyogen sequences which they may or may not arouse. May it not be that some of the failures are in those epidemics in which nontransmutable fixed or true viruses officiate, while in others the filterable agent in the naso-respiratory outbreak is transmutable into a pathogenic pyogen?

When one recalls the anomalous cultural results in explosive bullous eruptions of the hands and feet ("dermatitis repens") and in pustular psoriasis and when one reads the reports of Woglom and Warren (1938 1939) concerning a pustular eruption of the paws of rats due to pyogenic virus infection, one begins to wonder where dermatophytosis of the hands and feet with id manifestations really begins and ends.

As we have said before, we are only indulging here in a pernicious form of wishful, but stimulating, thinking. Perhaps we have said enough to induce the dermatologist to turn to the virus laboratory for some of his next advancing steps.

The psychogenic or psychoneurogenous mechanisms

We turn to this final topic with a sense of home-coming, for we have long been interested in the subject and it has flavoured or contaminated much of our thought. In fact we might be tempted to start all over again as neuro-psychiatrists, were it not that a fairly secure position outside that guild permits us an occasional shot or critical raid (in the fullness of our ignorance) upon the closed circle of the elect. We have so much and so recently reviewed the field (Stokes 1930 1931 1932, 1935 1940) (Stokes and Beerman 193., 1940) (Beerman and Stokes, 1934) (Stokes, Beerman, Ingraham, 1939 1940) that it seems unwise in this short space to repeat or to trespass on what will be better done by other contributors But a little clinical commentary may have critical value. From its beginnings with Theodore Sack (1933) (disregarding earlier sporadic contributors) the realization that many dermatological problems are psychosomatic (and many allergic problems too) has spread rapidly among clinical workers, and, as might be expected, has aroused hot discussion and some rocklike opposition. The problem which neuro-psychiatric investigation faces is similar to that we described under the flush mechanism, which is in part a neuro-psychiatric problem. Its conclusions are valid for the eye and judgement of the investigator (we had almost said the votary) but they just do not make sense to the commonalty The lack of objective mensuration, the paucity of experimental studies under anything like adequate controls, the fact to which among others we have called attention (Stokes and Beerman, 1940), that there exists no adequate study of normals for base-line comparative purposes and that much of the pathological material reported has too much of an I had a case quality all impede investigation and discredit conclusions. There is too the omnipresent ignorance on the part of dermatologists and psychiatrists of the elements of each other's terrain. There seems to be, too an exceptional distrust of the investigator's warp and prejudice in all things involving psychical appraisals The very word psychic carries dubious implications of charlatanism and art-magic of which we must certainly rid ourselves if real progress is to be made.

Notwithstanding these handicaps, progress has been made in defining personality states and patterns such as the EAHF (EAHF = Eczema—asthma—hay fever),

flora this probably establishes a streptococcal or other bacterial preponderance after the virus infection, that encourages the production and absorption of porphyrins, with their light-sensitivity inducing effects. The sequence is of interest, too in explaining exacerbations of pruritus ani with dermatitic perianal collarettes and with inguinal intertrigo Even catarrhal vulvovaginitis (*Micrococcus catarrhalis* infection) after naso-respiratory virus infections, can be included in a sequence of this sort The fungus pyogen sequence, to which Darier Ravaut, and their co-workers (Darier 1928 Ramel 1929 Ravaut and his colleagues, 1930) devoted so much stimulating research (levurids, streptomycotic intertrigo, and the Darier Ravaut Ramel syndrome) is an infection-allergic sequence of similar type with the widest significance as an explanation of the bacteriology of epidermophytosis of the feet and groins and so-called ids fungal and bacterial

It has been exceedingly interesting to watch the growth of the conception of naso-respiratory incitement of exacerbations in Besnier s prurigo neuro-dermatitis and to us the whole eczema—asthma—hay fever complex as illustrated in the recent papers of Norrlind (1946) and of Boe (1946) These investigators emphasis seems to us to be primarily upon the study of infection allergy to what in our virus-pyogen sequence ideas appear as secondary invaders, and upon the means of desensitization to them rather than to the primary sensitizing virus We too emphasize the use of very small doses very slowly advanced, in our use of staphylococcus toxoid and bacterial antigen for what we call a hyposensitizing as distinguished from a bacteriological immunization technique. But we are looking now towards a potent influenza virus vaccine for a preventive of the primary invasion by virus as an accessory or perhaps even a more fundamental approach to the virus-pyogen sensitization complex in these widespread affections.

Virus transmutations —This whole problem of virus-pyogen sequences and primary and secondary invaders is shot through with another fascinatingly suggestive group of phenomena thus far largely studied in the laboratory and insufficiently understood by dermatologists and others This is the transmutation of organisms from non filterable to filterable forms under as yet not fully under stood, but in part nutritional conditions. Tyrode s medium was employed by Kendall (1926) in producing filterable from typical non filterable forms of typhoid bacilli, the ictero-haemorrhagic spirochaete and other visible pathogens with established identities. Rosenow (1944 a b and c) has recently reported studies of a filterable infectious agent derived by various nutritional and cultural devices from pneumotropic streptococci which he reports as capable of reproducing in mice lesions identical with those produced by a known influenza virus. Jaquette, Convey and Pillsbury (1946) review the literature of the Kaposi varicelliform eruption and report the presence of the virus of herpes simplex—vaccinia virus had of course, long been suggested These authors intimate that streptococci and staphylococci are an essential part of the picture On the other side of the problem studies such as those of Rantz and his co-workers (1946) on epidemic naso-respiratory infection and streptococcal invasion, led them to the conclusion that the apparent increase of streptococcal complications after virus epidemics is fictitious and was due to the importation of streptococcal carriers into the personnel they studied We have ourselves realized the complexity of this problem, but have thought that we saw reason to believe that there is a difference between virus

makes crucial the study by hypnotic and other agencies of for example, the allergic weal reaction (Diehl and Heinichen, 1931) (Marcus and Sahlgren, 1936), and of physical allergy as well as what Duke (1927) called emotional allergy and we might now ally with cholinergic urticaria. We need also much more of the analytical take-down studies, such as Pearson's (1940), of the complexes underlying the inflammatory and infective dermatoses. Also we require more studies of the hyperventilation mechanism in connexion with the acute anxiety states of some eczema—asthma—hay-fever patients who are in vascular sweat and dermatitic crises, as one who watches their breathing can at times attest. Wittkower's (cited by Gillespie, 1936) and Gillespie's (1936) observations on this matter and Carryer's (1946) paper on functional disorders in relation to hyperventilation, are in point.

The hourglass sands, and our page and word limit, remind us that other fascinating fields for speculation must remain untouched by our discussion, our dithyrambics, even our diatribes. We enjoy to the full, putting knotty questions to others for solution Was it not the psychologist, William James, however who reminded us that to allow an emotion (like day-dreaming, wishful thinking and research rumination) to go untranslated into action is a form of emotional debauchery that leads to deterioration? Lest such a fate befall us, if we are not under its shadow already let us as dermatologists summarize and proceed with the work We should not be deluded into resting upon our glorious past or upon our numerically adequate future in the case rosters of medical practice There is desperate need—amounting to a risk of extinction of our specialty we fear through a re-engulfment by our parent, the mother-discipline of Medicine—if we fail in fundamental creative thinking and creative work in functional fields. To that end, let us select our trainees for fitness to attack basic problems with newly devised, or revived, significant and ingenious methods. Let us search the whole field of Medicine and the basic sciences bibliocritically for interrelations that may be significant for the behaviour of the skin, and for the light the skin can shed on the behaviour of the body Let us elevate the gifted observer of common things and sit down hard upon the sterile case reporter of one more of an inadequately and unimaginatively studied and too often unimportant rarity In so doing we shall emulate a distinguished tradition and use it to our good the tradition of MacKenzie and of Lewis, among others, who have found through simple instruments small numbers, penetrating thinking and intense study of the human being, the key to vast advances of knowledge. Thus shall we be spared destruction, or at least be made circumspect with regard to the risk of anoxaemia from suffocation by the sirens, organization (except of thought), big money in fellowships and foundations, and bricks, mortar and the sounding brass of equipment for our work.

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and the tension personality (Stokes, 1940) and notably in the direction of conflict, as in the Klaber Wittkower (1939) *social anxiety concept, which in our hands has,* with the resolving devices we have worked out to deal with it, changed the treat ment of the rosacea complex (Stokes and Beerman 1932 Beerman and Stokes, 1934) from an uncertain and vexatious affair of empiricism and relapse to one of comparatively *easy certainty and permanence. As one sees gastric* and duodenal ulcer the domain of the internist-dietician and the hard-boiled surgeon gathered into the psychogenetic fold the way is being paved for new studies of the psycho-dynamics *of the distraught mind The identification* of cholinergic urticaria and the definition of its mechanism is a notable advance (Grant *et al.*, 1936 Hopkins *et al* 1938) Emotional effects of spontaneous hypoglycaemia, and the pre-menstrual tension and progesterone hydration phenomena are still a little far out on the edge of available correlations but both have possibilities in the study of the pre-menstrual pyogenic flare and the so-called dermatitis dysmenorrhoeica for example

The induction of cutaneous reaction under hypnosis is a field deserving of much more study than it has been given and the invention of new techniques of by passing of the cortex in order to reach the lower suggestible levels of the brain more directly may open up a new field for the induction of dermatoses suspected of *psycho-neurogenous connexions (i e herpetic eruptions, cholinergic urticarias,* stigmatization allergic wealing, etc.) in which we may be able to delineate with almost photographic accuracy the processes in the mind and the linkages in the nervous system which produce, or better *constitute the psychogenetic component* in cutaneous *reactions To be sure there may be still sitting growling on the side,* the acupuncture brain physiologist, who insists that unless a reaction can be tested by destruction of a centre with his (sometimes) clumsy needle, there is nothing *to this thalamic stuff except the emotional patterns of the investigator*

In the phrase psychogenetic component lies much of the crux of the matter *Some will probably not be driven from the corner in which they* reiterate that they have never seen a purely psychogenetic dermatosis (barring, we assume, the hysterical self inflictions) The *multiple* conception of cause must imbue and impregnate the mind of every investigator of the psychogenous or he is warped from the start and indeed the same statement might be made of any would be dermatological investigator and of all investigators.

We referred parenthetically to allergy This deserves brief amplification as integral to the dermatological field Pre-war Europe had progressed chiefly in the field of asthma far beyond the United States of America in its study of what we now familiarly speak of *as the threshold-of reactivity factor in allergic response* To us there seems to be reason to believe that what we accomplish by suggestion and re-education for patients with combinations of allergic and psychogenetic factors is done, as Fock (1928) Moos (1928) and Hansen (1927) insisted for asthma, *by raising the reaction threshold* of the nervous system, without altering the allergic cellular response as such *Perhaps this is done by strengthening the* inhibitory function of the cortex in holding down the irritability or exuberance of *the sympathetic nervous mechanism* including the thalamus. Thus one talks the patient back into control of his reaction mechanism. It is work of this sort that

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CHAPTER 2

THE ANATOMY OF THE SKIN

G. WEDDELL

INTRODUCTION

THE skin is a complex and protean tissue the structure of which is inconstant from race to race, from individual to individual, and from region to region in the same individual. Furthermore, the structure of a given region fluctuates in response to changes of both its internal and its external environment. It is on these general considerations that the following chapter is based.

SURFACE CONFIGURATION

The surface configuration of the skin is mainly dependent upon the arrangement and type of the dermal connective tissue, and upon the degree of attachment of the dermis to underlying structures.

Generalized patterning of the skin

The dermal connective tissue is disposed in bundles which lie parallel to the surface of the skin and at right angles to each other. These bundles are composed of a varying number of elastic and collagen fibres. The collagen fibres have an undulating appearance due to the pull of the elastic fibres running with them. In certain of the composite bundles the proportion of elastic fibres is greater than in others. This arrangement gives rise to the innumerable fine furrows, the so-called tension lines, which indent the surface of the skin. These, by uniting and parting from one another form a mosaic pattern. The general direction of these furrows corresponds to the "natural" cleavage lines of the skin (Jones, 1941; Cox, 1941). An appreciation of the disposition of skin tension lines is of value when planning skin incisions, for a correctly placed incision along a line of "natural" cleavage will form a non-puckered inconspicuous scar when healed (Fig. 1).

Specialized patterning of the skin

The skin over the finger pads and the palm is specially modified in pattern. The distinctive ridges form concentric whorls, loops, and arches. This pattern remains constant throughout the lifetime of an individual, but varies from person to person, even in identical twins, and this fact, *inter alia*, leads Gates (1946) to conclude that every finger-print is unique and beyond the control of heredity. These facts provide the basis of the Galton system of identification of individuals.

In order to obliterate the finger-print pattern, the underlying dermis as well as the epidermis must be extensively destroyed. If the epidermis only is burned with acid or scraped away the pattern is reproduced with identical details when the skin regenerates (Chapel, 1946). The specific dermal tissues involved in the organization of the epidermal growth are, however, unknown.

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GROWTH AND REPLACEMENT OF THE SKIN

Histogenesis

In early foetal life the epidermis consists of only two layers of cells. The basal layer is composed of cuboidal cells which multiply rapidly. The peripheral

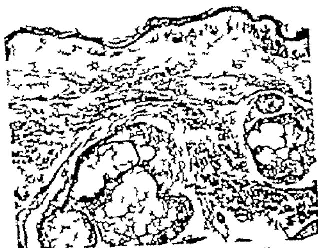


FIG. 3.—Skin from human forearm (× 60).

layer is composed of flattened cells, which are constantly formed afresh from the cells of the deeper layer. Later in foetal life an intermediate layer of cells appears;

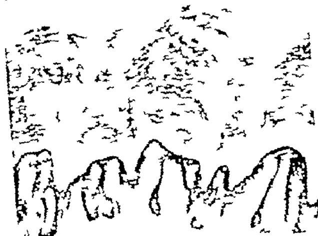


FIG. 4.—Skin from human finger (× 60). Note the great thickness of the stratum corneum and also the prolongations of the stratum germinativum into the dermis, giving rise to dermal papillae. This arrangement is related to an increase in thickness of the epidermis.

these cells are interconnected by protoplasmic bridges, forming a syncytium. Still later the number of distinguishable layers increases, and cornification occurs

Flexure lines

Besides the fine patterning of the skin there are skin furrows which are more obvious In certain regions, *such as the palm of the hand, the skin is firmly* attached to the underlying tissues. Here, skin joints are developed which allow the skin to fold easily in response to joint movements. The skin is also attached to

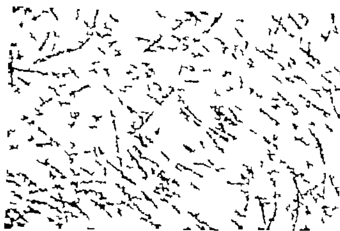


FIG. 1—A disfiguring scar which has resulted from an incision at right angles to the lines of natural cleavage in the skin (×).

the periosteum of bones where they approach the surface particularly in the neighbourhood of joints. These attachments may be responsible for the flexure lines which appear when the joint is moved They are not present in all positions of the joint in contrast with the skin creases of the palm, which are always visible. Indeed, the latter are formed before birth and not directly in response to movement In some cases dimples rather than furrows are produced Dimples are



FIG. 2.—Human foetal skin (× 450) from a 45-millimetre embryo

especially common on the face but in this instance they are due to the underlying facial muscles which are actually inserted into the skin It is through such attachments that many of the more delicate shades of facial expression are permitted In the later decades of life, when the connective-tissue framework of the skin loses much of its elasticity wrinkles appear *which are at right angles to the general* line of attachment of the muscles most commonly used.

GROWTH AND REPLACEMENT OF THE SKIN

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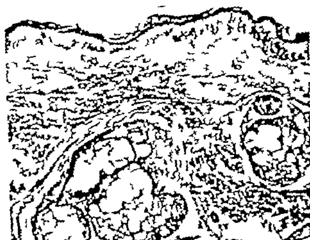


FIG. 3.—Skin from a human forearm (× 60).

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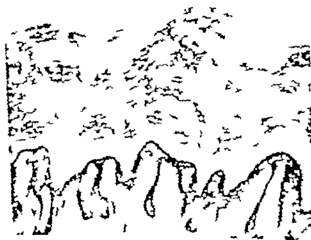


FIG. 4.—Skin from a human finger (× 60). Note the great thickness of the *stratum corneum* and also the prolongations of the *stratum germinativum* into the dermis, giving rise to dermal papillae. This arrangement is related to an increase in thickness of the epidermis.

these cells are interconnected by protoplasmic bridges, forming a syncytium. Still later the number of distinguishable layers increases, and cornification occurs

in the most peripheral stratum Even before birth the skin has essentially the same structure as in the adult although it is much thinner The deepest layer persists as the *stratum germinativum* superficial to which are the *stratum granulosum* and the *stratum corneum* The desquamated scales of the *stratum corneum*, together with sebaceous secretion and epitrichial débris, form the *vernix caseosa* of the foetus. (See Figs. 2, 3 and 4)

Normal replacement

Throughout life, new epidermal cells are being produced from the *stratum germinativum* and effete cells are being shed as degenerated squames from the skin surface. However the proliferative activity is intermittent and varies from one area of skin to another at any particular time Although there is an apparently rapid rate of renewal of the epidermis, there are surprisingly few mitotic figures to be



FIG. 5 —Forearm skin from a monkey (× 550). A cell is undergoing mitosis in *stratum germinativum* of the epidermis. The monkey from which this skin was removed had been injected with colchicine in order to stimulate cellular division.

seen in ordinary sections (Fig. 5) (Thuringer 1928 Carleton, 1934 Cooper and Schiff 1938 Cooper 1939 Cooper and Franklin 1940 Blumenfeld 1942 and 1943 Cowdry and Thompson 1944) This may be due to the fact that the epidermis is usually removed and fixed at a period when the rate of mitotic division is slow since it has been shown that a diurnal rhythm occurs in the rate of mitotic division. For instance, in the human prepuce the mitotic index (i e. the number of mitoses per standard number of cells counted) is lowest during the day and highest at night Besides mitosis, Ludford (1924) has shown that the cells of the epidermis may divide amitotically but this method of multiplication is not common Thuringer (1939) has investigated the effect of stimulation on the mitotic index of the epidermis of cats paws, using walking for a prolonged period as the stimulus. In such cases, the majority of mitoses are confined to the deeper part of the epidermis, but, rather unexpectedly more mitoses are found in the *stratum granulosum* that in the basal layer of the *stratum germinativum* He also observed that the different strata

respond independently. In the *stratum granulosum* the maximum mitotic activity occurs after one hour's stimulation, but in the *stratum germinativum* it does not occur until after two hours. Following the peak response, there is a decline in the number of mitoses in spite of continued stimulation.

In order to observe the growth reactions of isolated epidermal cells, the epidermis can be completely separated from the dermis. Such a separation also allows large continuous sheets of epidermis to be examined under the microscope. This greatly simplifies, for example, the counting of cells in an active state of mitosis (Cooper and Schiff 1938). There are several ways of separating the dermis from the epidermis. Menschell (1925), who was the first to separate the epidermis as a continuous sheet, macerated the skin in dilute acid. Baumberger



FIG. 6.—Elastic fibres stained with orcein can be seen anchoring the epidermis to the dermis (× 85).

Suntzeff and Cowdry (1942) have shown that sheets of pure living epidermal cells can be obtained by using either ammonia or heat under controlled conditions. Medawar (1941) has developed a further method of separation, which is based on the observation that the epidermis is anchored to the dermis by fine elastic fibres (Fig. 6). These fibres can be specifically digested by trypsin, so releasing the epidermis.

Age changes

The texture of the skin changes slowly from childhood to old age. The skin of a new born baby is very thin, but it becomes thicker with advancing age. In old age the skin is wrinkled, there are fewer tension lines visible, and it appears, on superficial examination, to be much thinner. The elasticity of the skin—as judged by pinching up a fold between the thumb and forefinger and letting go suddenly—also gradually changes as the latter decades of life approach, for the skin takes progressively longer to flatten and return to its previous state.

Evans, Cowdry and Neilson (1943) have shown that if the dermis is removed before fixation, the epidermis from an old subject appears to be only slightly

thinner than that from a young subject This difference is due to a tendency to lose one layer of the *stratum granulosum* in old age, and also to a slight reduction in thickness of the *stratum corneum* Evans and his colleagues have also shown that the striking difference in thickness of the epidermis in the skin of old and young subjects, which is usually noted in stained microscopic sections, is mainly an illusion due to distortion of the epidermis from shrinkage of the dermal connective tissue by the fixative this shrinkage is much greater in young skin (46 per cent) than in old skin (12 per cent)

The dermis is subject to age changes which are far more extensive than those affecting the epidermis Hill and Montgomery (1940) have shown that the areas of skin most affected are those which are exposed and subject to the greatest trauma. They have also pointed out that, in order to obtain a clear idea of the cause of the wrinkled inelastic skin of old age, the histological material must be stained specially for both collagen and elastic fibres. It will then be seen that the staining properties and disposition of the collagen fibres are altered in old age much less than are those of the elastic fibres

Factors controlling the growth of the skin

Hooker and Pfeiffer (1943) have shown that well marked atrophy of the epidermis in rats can be caused by the administration of oestradiol benzoate This change can be reversed by giving testosterone propionate. If an untreated animal receives the two hormones simultaneously however no change in the histology of the skin can be observed

Vitamins and other accessory food factors are essential for the normal growth of epidermal and dermal elements but their action on the skin is in no way specific. Cutaneous manifestations of vitamin deficiency are but readily recognizable signs of a disorder of growth that is also occurring in other tissues In the skin however changes may occur earlier since it is more exposed to numerous environmental conditions Vitamin A for example, is necessary for the normal growth and maintenance of all epithelial cells a deficiency of this vitamin causes hyperkeratosis and atrophy of the sweat and sebaceous glands Vitamin C influences the development of connective-tissue cells and the production from them of the extracellular matrix. One of the effects of vitamin C deficiency is a weakening of the capillary walls, with the formation of petechial haemorrhages. The haemorrhages may occur earlier from the cutaneous capillaries owing to their greater exposure to the aggravating effects of trauma A fuller account of the cutaneous manifestations of vitamin deficiencies has been given in an excellent review by Platt (1945)

Natural healing of the skin and skin grafts

The skin has a great capacity for regeneration and repair When the epidermis is removed provided that isolated patches of the *stratum germinativum* remain repair occurs rapidly by the proliferative activity of these fragments. If the wound is deeper a new covering of epidermis is formed over the denuded area by the active division of the epidermal cells at the margins of the wound In some cases, this natural repair process is inadequate to secure an efficient functional repair of the damaged tissue. In most instances skin autografts offer an adequate solution On occasions, however it is not possible to remove sheets of skin of sufficient size from other parts of the body to cover the wound. The only possible procedure,

then, is to graft the areas with isolated fragments of skin, a continuous epidermal covering being obtained by lateral extension from these fragments. Skin homografts have proved to be unsuccessful: they cause an inflammatory reaction in the tissues of the host and eventually undergo necrosis. As a result of skin-grafting experiments on rabbits, Medawar (1944, 1945) has produced evidence that the elimination of the *foreign skin* is due to the body actively acquiring an immunity towards the graft. The differences observed between the intensity of the homograft reaction from one pair of animals (donor and recipient) to another are explained by the degree of genetic variation between the animals.

THE COLOUR OF THE SKIN

The colour of the skin depends upon the disposition and amount of pigment in the epidermis and dermis, and also upon the volume of blood flowing through the cutaneous vessels. The colour so produced is modified by the thickness and the turbidity of the epidermis.

Skin pigmentation

There are five pigments involved in the coloration of the skin. Three of these, melanin, melanoid and carotene, are extravascular. The others are the oxyhaemoglobin and reduced haemoglobin of the blood. The relative amounts and concentrations of these pigments account for the variations of colour of the skin in different regions of the body (Edwards and Duntley 1939).

In the epidermis, melanin, which is the most abundant of the extravascular pigments, appears in the form of fine dark-brown granules within the cells of the *stratum germinativum*, particularly in its basal layer. As these cells are forced towards the surface, the pigment granules gradually disappear, so that only a diffuse pigmentation is observed in the most superficial epidermal cells. In people with very fair skins, melanin may be found only in certain cells of the *stratum germinativum*, but in those with darker skins, there are melanin granules in all the cells of the *stratum germinativum* and there may be some in the more superficial layers of the epidermis. Scattered amongst the cells of the basal layer are peculiar branched pigment cells, the melanoblasts. It has been suggested that these cells are derived from the basal layer of the epidermis and that they are specialized to produce melanin from a colourless precursor. The melanin which they produce is then passed over to the other epidermal cells. That the melanoblasts are specialized pigment-producing cells is indicated by the fact that when pigmented skin is grafted into a relatively non-pigmented area, the pigment of the skin surrounding the graft is greatly increased, probably because of the acceptance of pigment from the melanoblasts of the grafted area (Saxton, Schmeckebier and Kelley 1936). Billingham and Medawar (1947) confirm the observations made by Saxton *et al.* (1936), that the pigmented cells of the graft do not invade and replace the colourless cells. They suggest, however, that the increase in pigmentation is due to an agent (probably a self-reproducing body housed normally in the cytoplasm) which, having entered the unpigmented cells, brings about a permanent heritable change that causes them and their descendants to remain thereafter pigmented.

In the more superficial layers of the dermis, there are a few connective-tissue pigment cells, the dermal melanophores. The granules of pigment which these

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Even in the white races melanin is present in nearly all areas of the skin, but it is most apparent in certain localized regions, e.g. the nipple and the areola, and on and around the external genital organs.

Fluctuation in the degree of skin pigmentation occurs in individuals under certain conditions, but the factors which contribute to these changes are not well understood. Hormones, especially the oestrogens, are responsible for certain fluctuations in the degree of skin coloration. For example, during pregnancy the pigmentation of the areolae is increased and other areas of skin may become obviously pigmented. After parturition however the extra pigmentation recedes, although the skin seldom returns to its previous colour



FIG 8—Skin from cat paw (45) The blood-vessels have been injected with carmine-gelatin. The capillaries are at right angles to the surface of the skin and are draining into the superficial venous plexus, which is parallel to the surface.

Rapid changes in the degree of pigmentation take place in the skin beneath the eyes This is very obvious in children who when they are tired have dark crescents beneath their eyes. These disappear after they have had a good night's sleep In adults, the dark crescents are often permanent, but they vary in intensity according to the degree of fatigue of the subject. This phenomenon has not been satisfactorily explained, but it is possible that the dermal melanophores in this area behave in the same way as do the melanophores of lower vertebrates, although elsewhere in human skin they do not appear to undergo alteration in their shape or in the concentration of pigment granules which they contain.

Vascular colour

The vascular colour of the skin is not dependent upon the vessels closest to the surface, the capillary loops, but upon the venules of the most superficial venous plexus, which lie parallel to the surface (Wetzel and Zotterman, 1926)

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There are wide racial variations in the degree of skin pigmentation, and this can in some measure, be correlated with the normal habitat of the particular race. This might be expected since there is little doubt that the pigment in the skin serves as a protection from the ultra violet radiation of the sun There are, however some striking exceptions, such as the light skinned Fulani tribe of



FIG 7.—*Pigmented skin from a negro (× 550)* There are numerous cells laden with pigment in the deeper layers of the epidermis. A melanophore can be seen in the dermis.

Central Africa which are difficult to explain except on the basis of recent migration. Of course the pigmentation of the skin in dark races is inherited but even in these the degree of pigmentation can be modified by changes in environmental conditions.

Variations of the degree of pigmentation occur *in individuals of the same race*, which again may be associated with their environment For example among the white races in the summer months the exposed skin becomes tanned as the result of exposure to the sun s rays but during the winter months this tan is lost. However for some unexplained reason certain persons, especially those with very fair complexions and red hair never tan as the result of exposure to sunlight.

In albinos, there is a complete congenital absence of the extravascular pigments. Pigmentation is even lacking in the iris and retina Such persons cannot expose themselves to the sun without receiving severe burns Albinism is a curious

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of interest. Weiner (1945) has shown that there are marked regional differences in the amount of sweat secreted in response to high environmental temperatures but there are not sufficient anatomical data to determine whether these regional differences are due to an increased output of individual glands or to regional variations in their number. A modification of the sweating test might be useful in this respect.

There are a few individuals who have a congenital absence of sweat glands. Such persons may die of heat stroke if exposed to high temperatures, even for a short period. They suffer considerably on a hot summer's day and are incapable of taking strenuous exercise. It would be interesting to know whether there are people who have a smaller number of sweat glands than normal, and whether their thermal tolerance is reduced in consequence.



FIG. 9. Skin of the palm in a patient with an ulnar nerve lesion, following a sweating test. The orifices of the functioning sweat glands are indicated by the fine stippling along the papillary ridges. The continuous black line and large black dots are the boundaries of touch and pain loss, respectively.

Sebaceous glands

The majority of the ducts of the sebaceous glands open into the necks of hair follicles, but in glabrous areas, such as the lip and the glans penis, they are independent of hairs and open directly on the skin (Fig. 10). The secretory part of the gland, which lies in the dermis, is represented by several rounded sacs, which form a mass—like a bunch of grapes. Each sac opens into the main duct.

The oily secretion, or sebum, which results from the breaking down of the glandular cells themselves, provides a lubricant to the hairs. It also keeps the skin supple and forms, for both the skin and the base of the hair shafts, a protective coat which is relatively impervious to the effects of moisture and prevents desiccation. The sebum, in conjunction with the sweat, has certain bactericidal

Although the latter are on a deeper plane, they present a greater surface area than do the capillaries, which are disposed chiefly at right angles to the skin surface (Fig. 8) The facial skin for example actually contains fewer capillaries per unit area than does the skin of the limbs, although its vascular colour is usually more intense The variations in the tint and the depth of colour are due to the size of these venules and the rate of blood-flow through them The tint of the skin—that is the relative degree of the blue or red hue—depends upon the extent to which the oxyhaemoglobin is reduced in its passage through the cutaneous vessels, and this in turn is related to the rate of blood flow through the skin. The depth of colour is dependent upon the calibre and the degree of engorgement of the superficial venules.

These factors underlying the vascular colour of the skin are of considerable anatomical and physiological interest, and an appreciation of their nature may afford valuable diagnostic information An assessment of the vascular colour of normal and abnormal intact skin (either with the naked eye or by examination through a microscope) is of much more value in this connexion than is a study of biopsy material The latter can give no useful information regarding the pattern and degree of vascularization of the skin during life because of the inevitable distortion of the vessels caused by fixatives.

CUTANEOUS GLANDS

Sweat glands

The sweat glands are present everywhere, except on moist surfaces such as the lips They are simple coiled tubes, situated in the dermis, with narrow unbranched secretory ducts The cubical glandular cells lie on a layer of flattened spindle-shaped cells—the myo-epithelial cells. It is supposed that these cells, by contracting, help to discharge the secretion but it is undecided whether or not they are true unstriped muscle fibres for they are probably ectodermal and not mesodermal in origin The secretion of the sweat glands is not continuous but the sweat is discharged at intervals in droplet form This may be demonstrated by injecting intradermally a dilute solution (0·01 per cent) of methylene blue. The dye is taken up and concentrated by the glandular cells and can easily be seen discharging regularly in successive droplets

The sweat glands are dependent upon the sympathetic nervous system for their activity although it is interesting to note that their reaction to sympathomimetic and parasympathomimetic drugs is anomalous. The sympathetic secreto-motor fibres are associated with the cutaneous sensory nerves and supply corresponding areas of skin Sweat glands cease to secrete if their nerve supply is interrupted Making use of this fact, Guttmann (1940) has developed a method of mapping out denervated cutaneous areas To render the absence of sweating in an anaesthetic area readily visible, the skin is covered with quinizarin-starch powder a compound which changes from pale to dark blue on contact with moisture, and generalized sweating is induced by radiant heat (Fig. 9)

Although sweat glands are morphologically excretory organs, their most important role in man is temperature regulation heat being lost from the body by evaporation of the discharged sweat In this way the activity of sweat glands is of great importance in relation to the response of individuals to a tropical environment (Ladell, 1945) The distribution and number of the sweat glands is therefore

coarse hairs of the body may be conveniently grouped into three categories (Danforth, 1939). The first category includes the hair which is the same in both sexes and the growth of which is apparently uninfluenced by the sex hormones (for example, the eyebrows, the eyelashes, and the vellus). These hairs normally do not undergo a progressive change from childhood to old age. Hairs of the second category are those which are stimulated to coarse growth at puberty in both sexes for example the pubic and axillary hairs. Hairs of the third category are those which can be classed as a true secondary sex character. In this group may be included the male beard and, less clearly the coarse hair of the chest, abdomen, and limbs in the male. Although not all the hairs of the body can be assigned to one of these three categories (for many are intermediate in character), this classification emphasizes the fact that hairs are to some extent independent units with their own growth characteristics. This is well illustrated by the behaviour of full-thickness skin autografts before and after puberty. Before puberty skin transplanted from one area to another blends imperceptibly with its new surroundings. After puberty however it retains the character of the skin of the region from which it has been taken, and the result may be a patch of hairy skin surrounded by relatively hairless skin, or vice versa.

Besides sexual variations, there are well-marked racial and individual differences in the distribution, texture, and amount of homologous coarse hair. The explanation of these differences is not clear although heredity plays an important part in determining them.

Hair growth

Hairs undergo periods of active growth followed by periods when growth virtually ceases. Butcher (1935) has shown that, in young white rats, the total cycle of hair growth, from the formation of the hair bulb to its separation from the papilla, is 35 days. Half this period is taken up by active growth, and the other half by a state of quiescent maturity. It was also observed, on occasion that old hairs remained in follicles in which new hairs were growing, and that some follicles were occupied by as many as three hairs. In human adults, Trotter (1924) has shown that each hair has its own independent life cycle. For example, one area of skin which she examined contained 230 hairs, of which only 45 per cent were observed to grow over a period of two weeks.

Trotter (1935) has also demonstrated an apparent relation between the type of the hair and the growth cycle. She found, in a series of pregnant and post parturient women, that the follicles of small hairs in the lumbar region had a short period of growth and a long resting period, and that the pubic hairs, which were larger had growth and rest periods of approximately equal duration, whereas the perineal hairs, which were the largest of all, had slightly longer periods of growth than of rest.

Cycles of hair growth are remarkably regular despite minor fluctuations. The same hair follicle, over a period of years, will frequently show many cycles of almost the same length (Danforth 1939).

The rate of growth of a hair in the active phase varies with its diameter. Pinkus (1903) has estimated that a scalp hair grows at the rate of 2.8 millimetres a week.

properties and may thus act as a natural barrier against infection (Burtenshaw 1945) (See Chapter VIII)

The amount of sebum secreted varies from individual to individual, some people having more oily skins than others, but the factors controlling the secretion are imperfectly understood The activity of the sebaceous glands is not under the control of the nervous system (Doupe and Sharpe 1943) but the sex hormones do appear to have some effect on their behaviour This statement is based on the fact that the skin becomes more greasy in both sexes at puberty when there is a tendency for acne vulgaris to develop This condition is caused by the plugging of the orifices of the sebaceous glands, with subsequent infection of their contents It is uncertain whether this plugging is due merely to an increased rate of breakdown of gland cells or whether the cells change their orderly rhythm of development and break down in groups.



FIG 10—Sebaceous gland in the skin of the penis (× 150) The duct is opening directly on to the skin surface

HAIR

Distribution

Hair covers the whole of the body with a few exceptions, the only glabrous areas being the palms of the hands the soles of the feet parts of the dorsal aspects of the fingers and the toes, part of the external genital organs and the lips Over most of the body the hair is fine relatively unpigmented, and inconspicuous. This has been termed by Danforth (1925) the vellus Before puberty the only well developed hair is that on the scalp, and that of the eyebrows and the eyelashes, the so-called coarse hair

At puberty there is an increased growth of hair particularly in the axillae and over the pubes in both sexes, and on the face in the male This hair is coarse and, in this respect closely resembles that on the scalp After puberty the fine and

turning grey or white overnight, under the influence of emotional stress, no steps have been taken to exclude the possibility that, before the stress, the subject was in the habit of dyeing his or her hair with a water-soluble dye. This might easily be washed away by the perspiration resulting from the emotional effect of the experience.

NAIL GROWTH

Le Gros Clark and Buxton (1938) have demonstrated that the rate of growth is not the same in all digits, but that there is a relation between the length of the digits and the rate of growth of their nails the longer the digit, the faster the growth of the nail They have also shown that there is no truth in the statement that the nails on the left hand grow faster than do those on the right. There are considerable seasonal variations in the rate of nail growth. The average rate of growth of the thumb-nail of Europeans in winter is 95 microns per day and in summer 115 microns per day In those who bite their nails, the growth rate is about 20 per cent higher than normal. It is well known that temporary severe illness or local damage alters the degree of growth activity of the germinal matrix, and results in irregular transverse grooves on the surface of the nails, which move forward as they grow Gilchrist and Buxton (1939) have brought forward some evidence that the rate of nail growth is affected by nutrition, but the changes are too small to be of value as a nutritional index, as had been hoped.

THE LYMPHATICS OF THE SKIN

In most areas of skin the lymphatic capillaries are disposed in two fine plexuses. The more superficial is found just beneath the epidermis below the blood-capillary network, and from it arise blind projections which extend towards the skin surface. The superficial plexus drains into the second plexus, which is situated in the deepest layer of the dermis. The deep plexus, in turn, is drained by vessels with slightly thicker walls, which usually accompany the veins. Kampmeier (1928) has demonstrated that the number of lymphatic capillaries forming the plexuses is very great, and McMaster (1942) contends that it is impossible to puncture the skin, even with the finest hypodermic needle, without injuring some capillaries. Valves are few and far between in the superficial plexus, but more plentiful in the deep plexus. They are numerous in the vessels which drain the deep plexus. Owing to the paucity of valves, the direction of lymph flow in the plexuses is not confined to a particular path, but the lymph can move in any direction, its course being influenced by gravity and other physical factors. Forbes (1938) has shown that there is a free communication between the plexuses across the midline of the body His work also suggests that the plexuses probably form a continuous net work throughout the body Once the lymph has entered the deeper lymphatic vessels its course is determined by the numerous valves which are present.

The wall of a lymphatic capillary is formed of a single layer of thin contiguous cells, which abuts directly against the surrounding tissues. The cells, though lacking independent contractility are extremely elastic, so that the capillaries may be considerably distended without being ruptured. Pullinger and Florey (1935) have described collagen and reticulum fibres extending from the capillary walls

Trotter (1924) has observed that the hairs on children's legs grow at the rate of 1·42 millimetres a week but the growth rate increases slowly to 1 82 millimetres a week at the age of 40–45 years Axillary and pubic hairs grow at a steady rate of 2 2 millimetres a week after puberty and this rate is unaffected by age.

Shaving does not increase the number of hairs, their rate of growth or their coarseness (Trotter 1923) This is an important experimental finding, for women suffering from severe facial hypertrichosis should not be discouraged from shaving —the cheapest safest, and most effective way of removing superfluous hair Trotter has shown also that the persistent application of cold cream is without effect on hair growth this is a significant finding in relation to the use of cosmetics.

There are seasonal variations in the rate of growth of hair Eaton and Eaton (1937) observe that facial hair grows faster in warm weather than in cold and, in fact that the rate of growth can be correlated with the mean daily temperature. Confirmation of this is provided by von Voit (1930) who states that scalp hair grows faster from March to July than from August to February and by Danforth (1939) who finds that hairs on the back of the hand have cycles which are longer from October to May than from May to October

Hair pigmentation

This shows considerable regional specialization like the other characteristics of hair but the factors which determine the degree of pigmentation of individual hairs are unknown It is certain however that the pigmentation of a hair does not bear a direct relationship to the pigmentation of the skin surrounding it. The colour of the hair is clearly determined in part by racial and hereditary factors. There are two pigments involved in hair coloration granules of brown pigment (melanin) and a more diffuse red pigment Brown hair results from a mixture of melanin granules and the red pigment Grey hair is due to the absence of pigment and grey hair turns white as the result of the formation of air bubbles in the hair shaft. The age at which the hair turns grey or white is subject to wide racial as well as individual variations (Boas and Michelson, 1932) It is also significant that greying of the hair is usually unrelated to age changes in other tissues. Hereditary and endocrine factors play some part in the greying of the hair but the fact that the hair of a black rat can be turned grey by a diet deficient in pantothenic acid and that restoration of pantothenic acid to the diet turns the hair black once more, is of considerable interest (Unna, *et al* 1941)

It is commonly accepted that the sympathetic nervous system plays an important role in the greying of hair for it has been reported that hair has turned grey or even white overnight as the result of great emotional stress. Landois (1866) reviews the literature on this subject and states that he was sceptical of the statements until he saw a case himself which he proceeds to report It is difficult to credit the truth of such statements, for there are no apparent means by which the living hair follicle could in any way influence the excreted non-living exposed shaft. It is true that the base of a hair may have a widely different coloration from the more distal part, but the colour change is not an abrupt one, and certainly is not due to the influence of the follicle For instance it is well known that sunlight, by bleaching the hair will give such a picture. Hair can also be bleached or dyed by artificial means, and it is most significant that, in all cases reported of hair

plexus at the level of the cutaneous arterial plexus. The subpapillary venous plexus is formed of endothelial-lined tubes without muscle coats. As the venules are traced more deeply scattered muscle cells can be seen on their walls. Even the vessels of the deepest venous network are imperfectly clothed with smooth muscle fibres.

Occasionally the cutaneous blood-vessels are arranged in a more complicated manner with intercommunications between terminal arterioles and venules of the subpapillary plexus. In such cases a capillary network can be said to exist in the skin, in contrast to the more usual arrangement of a succession of terminal arterioles giving rise to capillary loops (Heimberger 1925). Direct communications are also found between arterioles and venules in the region of the cutaneous arterial network: these are true arterio-venous anastomoses, the arterioles concerned being heavily coated with smooth muscle fibres. Such communications are particularly common in the nail bed and pulps of the fingers and toes.

The cutaneous blood-vessels are supplied with motor and sensory nerve fibres, which reach the skin in company with the cutaneous afferent nerves. They are non-medullated and end as beaded nerve nets around the walls of the vessels. The nets are in every way similar to those which subserve pain in the skin. Each nerve net extends over a considerable length of vessel, and the nets from adjacent nerve fibres interweave with one another. Nerves can be seen ending on arteries, arterioles (particularly arterio-venous anastomoses), and the larger venules and veins, but not on the capillaries despite statements to the contrary. In the skin of the rabbit's ear after cervical sympathectomy a proportion only of the nerve fibres and their terminals supplying the blood vessels degenerate, and stimulation of the vessels still gives rise to nociceptive responses (Woollard *et al.* 1940). This suggests that pain-subserving, as well as vasomotor, nerve fibres end on the walls of the larger cutaneous blood vessels.

Although no nerve fibres end on the capillaries there are moniliform nerve nets with beaded terminals in the dermis which are in very close relation to both the capillaries and other superficial cutaneous blood vessels. These nets and terminals are known to subserve 'second pain' and may be the nerve fibres concerned with local vascular reflexes (*vide inf.* a).

Broadly speaking, the functions of cutaneous blood-vessels are three in number:

(1) Nourishment of the skin and its associated tissues under all environmental conditions.

(2) Regulation of the body temperature.

(3) Provision of part of a mechanism for defence of the body against injury.

The fulfilment of these functions demands an anatomical system which is very flexible and capable of fine control. The arrangements which are described above are capable of meeting these demands over a wide range of conditions. However Grant and Bland (1931) have shown that, in response to extremes of environmental conditions, even the anatomical pattern may alter. For instance the number of arterio-venous anastomoses in the skin of the rabbit's ear can be increased by continual exposure of the ear to cold. This great lability of the cutaneous blood vessels is also seen in pathological conditions, such as those following injury or the result of inflammation.

to surrounding tissues, and they express the view that these fibres serve to pull the capillaries open when the tissues are oedematous

The repair and regeneration of cutaneous lymphatic capillaries have been studied by inserting transparent chambers into the ears of rabbits (Clark and Clark 1932 and 1933) The insertion of the chamber damages a number of the capillaries, and these proceed to regenerate Undamaged lymphatic endothelial cells seal the ends of the injured capillaries, and then give rise to solid protoplasmic sprouts which gradually invade the damaged tissue As the sprouts move ahead, the lumen of the capillary gradually extends into them. Mitotic division can be observed in the endothelial cells of the invading capillaries. Regeneration of the lymphatic capillaries is always preceded by that of blood capillaries sometimes the latter are months ahead Clark and Clark explain this observation on the ground that the regeneration of the lymphatic capillaries is more easily interfered with by mechanical factors than is the case with the blood capillaries In addition they find that lymphatic capillaries are less labile than are blood capillaries, for the former send out fewer sprouts and anastomose less frequently On the other hand once formed the lymphatic capillaries are more stable in size and shape than are the blood capillaries In the course of regeneration lymphatic capillaries are formed only from existing lymphatic endothelial cells Presumably similar changes take place in the skin of man following an injury

THE BLOOD SUPPLY OF THE SKIN

The number and size of the blood vessels supplying the skin vary in different regions of the body For instance, the skin over the palms of the hands soles of the feet ischial tuberosities, and other regions which are often subject to pressure in the course of daily life, have a particularly rich blood supply

The arteries supplying the skin form a network just beneath the dermis, and it is, in particular the size of the mesh which is decreased in the more vascular regions From the cutaneous arterial network arched and branching vessels arise, which extend towards the skin surface and together form the subpapillary arterial plexus From this network arise terminal arterioles, which run for a short distance parallel to the skin surface, sending twigs to the arterial limbs of the capillary loops. The capillary loops extend vertically as far as the epidermis. Lewis (1927) states that a terminal arteriole supplies a skin surface of approximately 0 16 square millimetre

The arteries of the cutaneous arterial network possess thick muscular coats, which however become thinner relatively abruptly about the middle of the dermis. Here, the vessels are clothed by a single layer of muscle cells As the arterioles are traced further towards their terminations, the muscle layer becomes less perfect, although muscle fibres can still be found at intervals on the terminal arterioles (Spalteholz, 1927)

The venous limbs of capillary loops drain into the subpapillary venous plexus. This consists of two freely communicating plexuses, lying parallel to the skin surface and just superficial to the correspondingly named arterial network The blood drains more deeply by numerous vessels into another venous plexus lying immediately below the subpapillary arterial plexus this in turn drains into a final

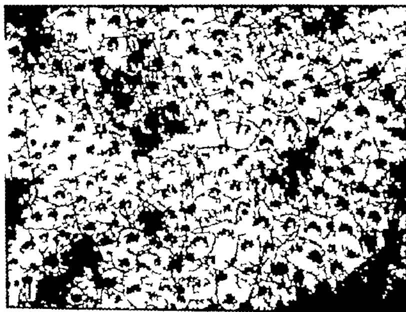


FIG. 11A.—Skin from rabbit ear (× 9) stained with methylene blue, showing the general pattern of innervation. Cells of the hair follicles also take up the dye.



FIG. 11B.—A higher-powered view of a portion of the same preparation (90). Individual nerve fibres, some of which are fine and beaded, can be seen.

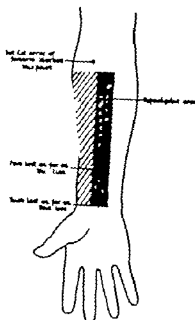


FIG. 12.—The effect of blocking the lateral cutaneous nerve of the forearm with local anaesthetic. The hypoalgetic zone and the touch boundary-line occupy exactly the same position if the medial cutaneous nerve is blocked. This experiment suggests that the terminal ramifications of the pain fibres are large and those of touch small.

Some of the cutaneous blood vessels in man can be studied directly under the binocular microscope. The skin is dehydrated with alcohol covered with cedar wood oil or paraffin oil and illuminated by a brilliant source of white light, which is filtered using infra red and ultra violet screens (Lewis, 1927) By this means capillary loops can nearly always be sharply focused and the subpapillary venous plexus can be seen a little less distinctly In addition if the skin is blistered and the cornified layer removed before examination the subpapillary venous plexus and terminal arterioles can be studied These methods can be used to determine the superficial vascular pattern in selected skin diseases, particularly those with distinctive vascular colours.

THE INNERVATION OF THE SKIN

The skin is the most extensive and varied of the sense organs, It is in direct contact with the outside world and thus enables the body to adapt itself to environmental changes. To subserve this function it is abundantly supplied with nerve fibres many of which bear specialized receptors. In addition it contains nerves which supply the blood vessels, cutaneous muscles, and sweat glands.

The cutaneous nerve fibres and their terminations are not selectively stained by the standard methods, and the special techniques which have been used until recently have been very unsatisfactory Consequently advances in this field of anatomy have been slow With the advent of a reliable technique for staining nerve fibres intravitally with methylene blue our knowledge of the anatomy of cutaneous innervation has rapidly expanded, since by this method it is possible to visualize selectively the nerve fibres and their terminations, and so to determine the general pattern of their distribution in large areas of skin (Figs. 11a and b)

It has now become apparent that in common with other skin elements, cutaneous nerve fibres and their terminals suffer continual damage as the result of the small traumata of everyday life. In any given area of skin a small number of nerve fibres can be seen undergoing degenerative or regenerative changes. In areas where such damage is at a maximum such as that over the point of the elbow the majority of persons have a small zone of altered sensibility in some case amounting to anaesthesia Skin from this region shows degenerating and regenerating nerve fibres in profusion (Weddell and Glees, 1941) Such changes, of course, are not confined to the terminal nerve fibres and endings in the skin but are to be found to a lesser extent in muscle and in other tissues which are liable to injury Naturally however they are much greater in the skin than in the deeper tissues, because of its exposed position It has also been found that the fine non medullated nerve fibres in the skin are particularly labile under certain circumstances. For example, if a peripheral nerve is cut, the denervated area of skin will be invaded by newly formed sprouts from those nerve fibres which are present in the surrounding normal skin (Weddell Guttmann and Gutmann, 1941)

The density of cutaneous innervation varies from place to place. Over the finger pads, for instance, it is greater than over the glans penis. Although of considerable functional significance the morphogenetic factors responsible for these arrangements are not understood

Woollard *et al.* also demonstrated that the nerve fibres coming from encapsulated sensory endings in the skin were always accompanied by accessory fibres bearing beaded terminals, similar morphologically to those which give rise to pain elsewhere. They suggested that their presence might serve to prevent over-stimulation of the organized endings by signalling the advent of potentially harmful stimuli. This finding also helps to explain the ubiquity of pain spots in the skin.

Weddell (1945) has shown that, in man, cutaneous pain is subserved by myelinated and unmyelinated nerve fibres, with terminal ramifications, which cover large areas and consist of moniliform nerve nets from which small beaded terminals arise (Figs. 13a and b) These nets interweave with one another and give the

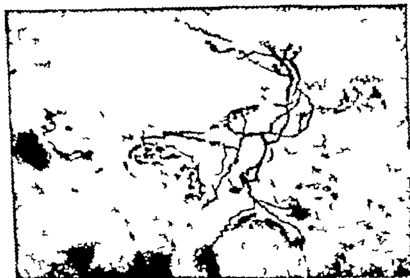


FIG. 14.—A spray of Krause end-bulbs subserving cold (human forearm). Methylene blue preparation (125). (*By courtesy of the British Medical Bulletin*)

appearance of a continuous meshwork of nerve fibres lying beneath the skin surface It now seems certain that cold is subserved by Krause end-bulbs and touch by Meissner's corpuscles, as well as by Merkel's discs and by hairs. Pressure is subserved by Pacinian corpuscles. The position as regards warmth is not so certain, but unpublished observations (Weddell) suggest that von Frey's contention that it is probably subserved by Ruffini's nerve endings is correct (Figs. 14 and 15)

The pattern of cutaneous innervation

Weddell (1941) has shown that sensory nerve terminals are arranged in the skin in a characteristic manner The cutaneous nerves enter a most intricate plexus when approaching their destination and become redistributed, so that they enter any localized area of skin from all directions. This explains why a simple incision through the skin, which does not involve subcutaneous nerve trunks, does not lead to an area of anaesthesia distal to it.

The territories of skin supplied by individual peripheral nerves are *not sharply* demarcated from one another but overlap to a varying degree (Woollard Weddell, and Harpman 1940) In some regions such as the finger pads, the degree of overlap is very small in other regions, such as the forearm (Fig. 12), it is larger

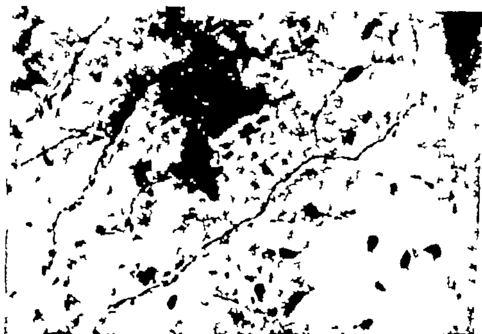


FIG. 13a.—Pain-subserving nerve net. Methylene blue preparation of skin from a human forearm (× 500). (*By courtesy of the British Medical Bulletin*)

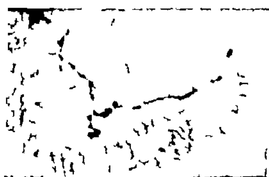


FIG. 13b —Pain terminal just beneath the epidermis, the basal cells of which can be seen faintly outlined Methylene blue preparation from a human finger (× 600).

Punctate sensibility

von Frey (1897) brought forward much evidence that the skin consists of a mosaic of small areas, which give rise to single sensory modalities when stimulated Woollard *et al* went further and showed that some of the observations which von Frey found difficult to reconcile with the theory of punctate sensibility could be explained by the fact that specific receptors lie at different depths beneath the skin In other words, *the theory of punctate sensibility must be interpreted from a three-dimensional point of view*

The principle of the multiple innervation of cutaneous sensory spots has also been established by Weddell (1947). He found that in the finger pad there are groups of Meissner's corpuscles innervated by separate unbranched fibres approaching them from different directions (Fig. 16) Similarly cold spots are represented by clusters of Krause end-bulbs borne upon separate fibres, and each hair follicle is supplied by two or more sensory nerves which approach from different directions (Fig. 17) This complex arrangement provides a mechanism for localization and for the discrimination of stimuli of different intensities. Multiple innervation of sensory spots is also of importance for understanding the process of sensory recovery after section of a cutaneous nerve. Sensory recovery is never abrupt in re-innervated areas of skin Head described two distinct phases



FIG. 17 —Hair follicle innervated by nerve fibres approaching from different directions. Silver preparation of skin from rabbit ear (× 230).

of recovery protopathic in which sensations are crudely felt, are diffuse, and have no quality of gradation epicritic in which sensation is discrete, accurately localizable and in which gradation can be appreciated (Head, Rivers, and Sherren, 1905). He believed that the two forms of sensation were subserved by different sets of nerve fibres which regenerated at different rates. Trotter and Davies (1909) failed to confirm many of Head's findings, however and no anatomical evidence has been adduced in favour of the existence of two sets of cutaneous nerves and receptors. In view of the pattern of innervation and of the multiple innervation of cutaneous sensory spots, Head's observations can be explained on a different basis. Weddell (1942, 1945) has shown that, during the course of regeneration nerve fibres in the skin arrive at sensory spots at different times, because the ultimate course of the fibres, approaching these spots from different directions, are of different lengths When sensation is protopathic in type, hair follicles

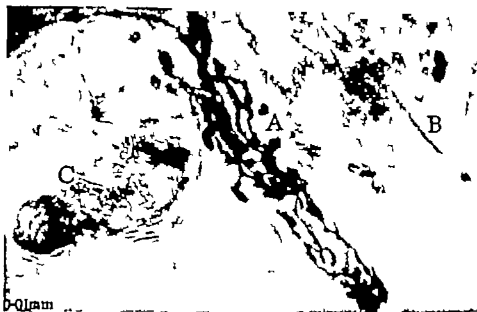


FIG. 15.—A = a Meissner's corpuscle in a human finger pad.
B = nerve fibre giving rise to a beaded pain-subserving nerve net.
C = sweat gland duct. (*By courtesy of the Journal of Anatomy.*)

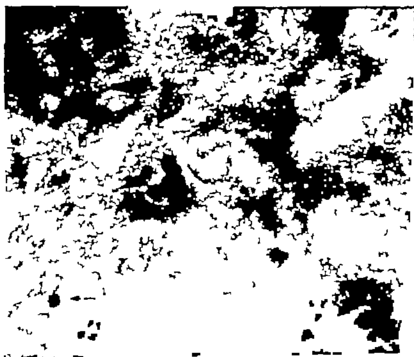


FIG. 16.—Methylene blue preparation of skin from a human finger pad (surface view of whole preparation). The arrows indicate Meissner's corpuscles, which are in groups. (*By courtesy of the Journal of Anatomy.*)

smaller blood-vessels, being subserved by non-myelinated nerve fibres and conveying slow pain The deeper network of pain-subserving nerve terminals almost certainly forms the anatomical basis for the local axon reflexes in the skin which have been demonstrated by Lewis (1936) and for which he postulated a set of nerve fibres termed the nocifensor system ').

Fig. 18 summarizes, in diagrammatic form, the innervation of skin from the pad of a human finger

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are innervated by solitary nerve fibres, and single Meissner's corpuscles can be seen as well as isolated nerve nets subserving pain. Later when sensory recovery is complete (that is to say 'epicritic') multiple innervation of cutaneous sensory spots can again be seen. Head's observations can thus be explained on the basis of the changing pattern of innervation during regeneration, and not on the existence of two separate peripheral nervous systems.

The 'nocifensor' system

Reference has already been made to the existence of large pain-subserving nerve terminals, which as the result of interweaving, form an apparently continuous

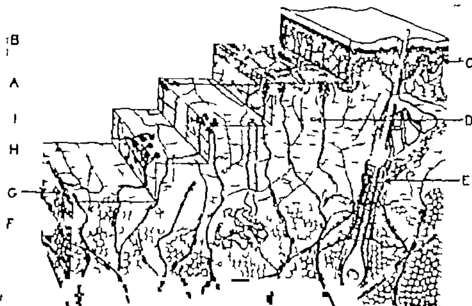


FIG 18.—Diagram illustrating the innervation of skin from the pad of a human finger. A = groups of Meissner's corpuscles subserving the sensation of touch. B shows beaded nerve-nets subserving pain (probably fast pain). C shows Merkel's discs subserving touch. D shows beaded nerve fibres derived from nerve nets subserving pain and associated with blood-vessels (slow pain). E shows nerve-terminals around the sheath of a hair subserving touch. F shows a Pacinian corpuscle subserving pressure. G shows a group of Ruffini endings subserving warmth. H and I show groups of Krause's end-bulbs subserving cold (these lie at somewhat variable depths beneath the skin-surface). Note the organized endings are accompanied in every instance by fine-beaded nerve fibres subserving pain. (*By courtesy of the 'British Medical Bulletin'*.)

network immediately beneath the epidermis. In certain cases of peripheral nerve injury or under experimental conditions in animals, the number of nerve fibres supplying an area of skin becomes reduced, so that the extent of a single terminal can sometimes be estimated. On the back of the hand Weddell (1941) found that one such terminal extended over an approximately circular area 0.75 centimetre in diameter. Weddell (1945) has shown also that the interweaving nerve nets situated below the epidermis can be divided into two groups, those closest beneath the epidermis being subserved by myelinated nerve fibres and conveying 'fast pain', and those deeper in the dermis, the terminals of which are in close relation to the

CHAPTER 3

PHYSIOLOGY AND FUNCTIONAL PATHOLOGY OF THE SKIN

G R. CAMERON and R. H D SHORT

PHYSIOLOGY AND FUNCTIONAL PATHOLOGY OF THE SKIN

Existing knowledge of the physiology of the skin is relatively small and, in the following account, emphasis has been chiefly laid upon those aspects which have received most attention. In other branches work has often led to inconclusive or confused results, which have been briefly summarized. No attempt has been made to describe the emotional aspects of skin physiology

Size of skin

The skin is an extensive organ whose weight is estimated at 16 per cent of the body-weight in an adult. Muchow (1925) gives the following figures

	Body-weight grammes	Body-surface sq cm	Weight of skin grammes
New-born child	3×10^3	2.6×10^3	$5 \times 10^2 \pm 50$ per cent
Adult man	7×10^4	2×10^4	$1 \times 10^4 \pm 30$ per cent

Naturally there are great variations. The ratio of body-surface to body-weight in man may be illustrated by the following figures

	Body-weight kilograms	Body-surface sq. cm.
1 day old child	3·2	2,999
6 months old child	7	4,381
14 years old child	38·6	13,670
25 years old adult	62·9	18,936

From such data Vierordt (1906) obtained the equation $S = 12.312G^{2/3}$ where G = body weight in grammes, S = surface in square centimetres For children and boys the constant is more likely 11·97

The thickness of the skin varies considerably throughout the body thus, in a 56 years old male described by Muchow the epidermis of the forehead was 0·059–0·087 millimetre in depth between the papillae, with a *stratum corneum* of 0·021–0·023 millimetre in the cheeks, the corresponding figures were 0·081–0·105 millimetre with a stratum corneum of 0·030–0·040 In the palm of the hand the epidermis was 0·487–0·651 millimetre its stratum corneum being 0·425–0·500 and in the sole of the foot the epidermis was 0·600–0·725 above the papillae with

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The capillary membrane is freely permeable to water and crystalloids at low pressures, but holds up most of the plasma protein. Consequently the latter can exert its osmotic pressure within the capillaries. This, though small (36 centimetres of water), is effective in attracting fluid and crystalloids from the tissue spaces The hydrostatic pressure averages 45 centimetres of water in the arterial capillaries and 22 centimetres of water in the venous capillaries. Hence, in the arterial portion the capillary pressure exceeds the colloid osmotic pressure of the proteins but in the venous portion the osmotic pressure is greater than the venous capillary pressure. Because of this gradient, a to-and-fro movement of water and crystalloids is ensured. There is also a small tissue pressure of about 2–5 centimetres of water which opposes the filtration pressure slightly and limits to some extent the amount of distension by fluid output. In some parts of the skin (for example the eyelids) the tissue pressure is so low and so little affected by increasing tissue fluid that oedema is common (" puffy eyelids ")

The lymphatics of the skin, which are very numerous beneath the epidermis (see below), are responsible for removing protein-rich fluid though they can deal with other substances of high molecular weight. An ultrafiltrate is easily re absorbed by the capillaries, but protein can be removed only through the lymphatics. No doubt the osmotic pressure of the lymph within these vessels is mainly responsible for keeping up the flow

The normal distribution of water and electrolytes in the skin is still undecided, especially in the case of man. Water comprises 65 per cent of the entire body weight, skin contributing 6–11 per cent, muscle 50 per cent. Adult skin is composed of 72 74 per cent water infant skin contains more water than adult skin (Weidman, 1942) and that of the females of some species more than the males (Hald, Giddings, and Wynn, 1943) Recent total skin analyses by Eisele and Eichelberger (1945) provide the following mean values per kilogram fat-free skin water 717 7±20·1 grammes, chloride 79 9±4 8 millimolar sodium 93·0±8 0 mM potassium 16·47±3 36 mM calcium 2·68±0·52 mM., magnesium 2 13±0·3 mM. The total nitrogen amounts to 45 5±3 8 grammes, of which 37 7±4 5 grammes are collagen nitrogen. The weight of connective tissue in human skin is estimated at 546±73 grammes per kilogram of fat-free skin, and the water-content of this connective tissue is calculated as 330±45 grammes. The volume of available water in skin is considerably larger than that in any other tissue of the body Cornbleet *et al.* (1942) give an average potassium-content in man of 247·0 milligrams per 100 grammes of dry weight, calcium 42 8 sodium 350 grammes. In normal adult dogs the total water-content is 708 3±20 1 grammes per kilogram fat-free tissue, the chloride-content 86 7±2 5 mM. per kilogram fat-free tissue, sodium 96 5±4 2, potassium 22·4±2 7 calcium 2 54 magnesium 3·03 (Eichelberger *et al* 1943) Total nitrogen amounts to 46 8 grammes, collagen nitrogen 33 1 grammes. In pregnancy the water-content increases. These figures, of course, refer only to stored or stationary amounts, for water and salts are constantly lost from the skin as well as withdrawn when depletion of the blood occurs. Thus in chloride starvation the blood chloride is preserved almost unchanged, but as much as 90 per cent of the chloride lost from the body may come from the skin. After the intravenous injection of hypertonic salt solution into dogs, the skin takes up large amounts of chloride which it may retain for as long as four hours (Gereb and Laszlo, 1930)

a stratum corneum of 0 525–0·600 millimetre. There is much variation, too, in the dermis, the laxity and vascularity of which are well known in certain parts of the body

Figures for the blood content of the skin in man are apparently not available, though Wollheim (1931) states that the subpapillary network between the end capillaries and the subcutaneous tissue can hoard as much as 1 800 cubic centimetres of blood or 30 per cent of the total circulating blood Too much stress must not be placed on such a figure however for it obviously refers to extremes of blood immobilization Lehmann (1925) states that the blood content of the skin of rabbits is 2 10 per cent of the total blood volume, muscle being 29 20 per cent and liver 29 30 per cent. Presumably all such figures refer to a resting, stable condition With increased heat production by the body the superficial vessels dilate, so that a greater surface of blood is exposed to the cooling effect of the surrounding medium (Pembrey 1910) A subtle control intervenes when the environmental temperature is high and loss of heat by radiation is restricted, whereby the sweat glands are brought into action and cooling is provided by greater evaporation.

Structural and functional variations in the skin

Desquamation of epidermis is a well known phenomenon and has been placed at 6 grammes per day by Funke and 14 35 grammes by Moleschott (1881) These figures need confirmation. Such a loss means regular replacement of the stratum corneum through cell transformations in the deeper layers of the epidermis, especially the stratum malpighii Mitotic division is a feature of this region and there is evidence that it is rhythmical in animals and man (Hirsch 1931 Carleton 1934 Cooper and Schiff 1938 Broders and Dublin 1939) Division is said to be more active at night than in the day at any rate in some regions, such as the foreskin Little is known about the factors regulating cell division in the epidermis beyond those appreciated during wound healing (see below) but there is some reason to believe that products released from dying or dead epidermal cells may serve as stimuli for division

Vascular variability is, perhaps, the most striking feature of skin (see below) of prime importance in the regulation of body temperature and body water it also underlies the essential phenomena of defence. There is a constant interchange of fluids and electrolytes between the blood and the tissues of the skin. A small amount of protein also leaves the vessels, being utilized for growth and repair of epidermal and dermal cells The essential nature of this exchange was clearly stated by Starling (1895–6) in terms of physical factors such as filtering or hydrostatic pressure in the vessels, osmotic pressure and membrane permeability of capillaries

The factors controlling the movement of fluid between the skin proper and vessels are

(1) the total area of filtering surface available, that is the capillary bed which amounts to many square metres

(2) the permeability of the capillary membranes

(3) the pressures exerted on the fluid inside and outside the membrane

(4) the osmotic pressure of the plasma proteins.

takes place nearer the surface in the *stratum granulosum* whilst Hou (1930) believes it to be a superficial process A great deal more work requires to be done on this important subject (see Bills, 1935, for review).

Vitamin A, a lipoid-soluble compound, can also be absorbed through the skin (Mandelbaum and Schlesinger 1942). Vitamins are said to be excreted in the sweat, thiamine, riboflavin, pantothenic acid, and nicotinic acid being instanced (Cornbleet *et al.*, 1943 Tennent and Silber 1943) but more careful work suggests that only nicotinic acid is present in human sweat in appreciable amounts (Mickelsen and Keys, 1943).

Little information exists about the elasticity of skin. Thus Wöhlisch *et al.* (1926) state that the modulus of elasticity is low in comparison with that of human tendon. It is, however similar in epidermis and dermis, but with stretching of the skin it rapidly increases and is finally eight to nine times as great as that of the dermis (40 kilograms per cubic millimetre as against 4 3 kilograms per cubic millimetre). The breaking stress in kilograms per cubic millimetre for skin—that is, dermis plus epidermis—is 180 as against 450 for human tendon. No doubt much depends on the basement membrane which is made up of closely-knit collagen and elastic fibres attached to loop-like processes of the last layer of epidermal cells (Patzelt, 1925). The skin thus includes a component which offers little resistance to expansion, but can sustain much tension. These features are brought into action in oedema. Histological changes in the elastic tissue of the skin with aging and other conditions have been studied by Inouye (1931–2), Jochims (1934), Ackmann (1935), and Hill and Montgomery (1940). The elastic tissue of the dermis gradually increases and later decreases just below the epidermis in the precancerous state (Willis, 1944).

The distensibility of skin has also been calculated in an ingenious fashion by Sodeman and Burch (1938). The normal mean distensibility of the pretibial area is 0·31 millimetre per centimetre per 100 grammes, for the dorsum of the foot 0·59 for the midline of the abdomen below the umbilicus 2·07 for the dorsum of the hand 1 34. Oedema, certain vascular diseases, and some dermatoses diminish the skin distensibility Such a loss is an important limiting factor in oedema formation.

Keratin is not an efficient conductor In the case of hair the conductivity is given as 0·000125 calorie per second and degree with silver it is 1·006, hence hair possesses $\frac{1}{8000}$ the conductivity power of silver (von Frey and Rein, 1929). This poor conductivity of hair (and fur) results in an insulation effect whereby heat dissipation is inhibited.

Protective function of the skin

The ability of the skin to protect against the weaker forms of mechanical injury and to some extent to insulate the organism from its environment, is due, to a large extent, to the properties of the stratum corneum. It is a poor conductor of heat. Mendelsohn and Rosster (1944) have shown that temperatures between 45° and 55° C. produce the milder forms of irreversible damage in skin and indeed in other tissue cells (Leach *et al.*, 1943). Coagulation necrosis occurs between 50° and 60° C. Skin is also a bad conductor of electricity (Lewis and Zotterman, 1926–1927) though exposure to the enormous voltages of lightning may result in the characteristic arborescent markings. These appear to be due to liberation of

There is evidence, too that sugar may be stored temporarily in the skin when there is hyperglycaemia later diffusing back into the blood-stream (Folin *et al.*, 1927) The dextrose value of skin is estimated at 60 2–81 5 milligrams per 100 grammes by Cornbleet (1940) but Urbach (1945) says the mean is 58 milligrams, and the value is rarely greater than 65 5 milligrams per 100 grammes. Cornbleet maintains that the dextrose-content is dependent on that of the blood, and that the rate of glycogen metabolism is similar to that in muscle, but different from liver Urbach (1945) describes a condition in which skin sugar alone increases, associated with furunculosis, sweat gland abscesses, eczema and a normal blood-sugar curve.

The hydrogen-ion concentration is fairly constant in the same skin area but changes throughout the body Harry (1942) gives an average *p*H of 5·4 for males and females. Draize (1942) records a maximum *p*H of 4 70 in white males and a minimum of 6 26 The maximum for white females is 4 70 the minimum is 6·66. Clearly the conditions governing reaction must be very complex. Marchionini and Hausknecht (1938) emphasize the importance of this acid cloak in defence against infection.

The pigment of the skin is well known to be of great importance in the absorption of ultra violet rays. White skin is more permeable to these rays than the skin of a negro the latter absorbing practically all rays of the shorter wave-length (Macht *et al.*, 1928) This screening effect is suggested by the orientation of melanin granules between the nuclei and the external surface of epidermal cells in the horse (Ludford 1924) Cutaneous melanoblasts are far more numerous in negroes than in white people (Niedelman 1945) The origin of melanin is still uncertain for a tyrosinase has never been conclusively demonstrated in the skin of mammals for the conversion of tyrosin into melanin nor does dopa (3 4-dihydroxyphenylalanine) occur in animal proteins Recently Rothman (1942) has claimed that tyrosin can be transformed *in vitro* into dopa by mild ultra violet radiation provided that small amounts of ferrous salts are present Ascorbic acid helps in the first stages of actinic oxidation of tyrosin though it completely inhibits any further oxidation There is complete inhibition of oxidation of tyrosin by tyrosinase in the presence of glutathione but oestrone in equivalent amounts abolishes the inhibitory reaction Oestrogenic hormones are well known to lead to darkening of the skin, especially the nipples of certain experimental animals, and it may be that oestrone releases tyrosinase in the cell from the inhibitory effect of sulphydryl groups. Further discussion of the function of melanin will be found below

It has long been known that ultra violet rays exert a beneficial action on persons suffering from rickets this is due to the activation of sterols in the skin (Hess, Weinstock and Helman 1925) The human epidermis contains 18 3–19 5 per cent cholesterol 90 per cent of this being uncombined cholesterol (Eckstein and Wile, 1926) Sterols develop anti rachitic potency on exposure to ultra violet rays (Hess, Weinstock, and Helman 1925 Steenbock and Black 1925 Rosenheim and Webster 1925) The anti rachitic activity is due to ergosterol which is a pro-vitamin from which calciferol or vitamin D_2 is formed (see Hou 1930 Hou and Tso 1930 Goldblatt, 1931) Anti-rachitic agents can be absorbed through the skin (Hume *et al* 1927 Taylor *et al.*, 1931) so that the oily secretions when irradiated may contribute to the vitamin stores. The exact site of activation is not known. Hess *et al* (1925) refer it to the prickle cells Bachern (1929) says it

Attempts to modify the healing time of wounds by hormonal activity have been inconclusive. Ceccarelli (1930), using direct application of extract of the anterior pituitary found no shortening of healing time, in spite of acceleration during the first week. Lauber (1933) noted rapid healing with hypophysin and prolan, males reacting more slowly to the latter Voronoff and Bostwick (1918) and Aievoli (1923) found accelerated healing when extracts of thyroid were applied to the wound or were injected. Conversely removal of the gland delays healing (Merlini, 1928) many other observers agree.

Melina (1933) found that local application of parathyroid extract produced early repair which was delayed by removal of the gland. With injection of therapeutic doses, Lauber (1933) found delay in the later stages.

There is evidence that direct application of suprarenal extract promotes healing (Lauber 1933) by favouring the growth of rich granulations (Voronoff and Bostwick, 1918 Aievoli, 1923) and that removal of the gland delays healing. If however the amount of hormone is increased by administration, gland transplants or various types of stimulation of the gland, the healing period is prolonged (Kondoba, 1934). Removal of the gland does not alter healing time.

Direct application of pancreas tissue delayed or stopped healing in the experiments of Voronoff and Bostwick (1918) and of Aievoli (1923). Using insulin, Lauber (1933) found no difference, but with the vasodepressor principle wound repair was assisted. In man, insulin appears to have a beneficial effect upon indolent ulcers, and extracts of the vasodepressor principle have been used in Raynaud's disease.

Pioneer work with testis tissue was done by Aievoli (1890), who reported more rapid healing when the tissue was applied directly no influence being found upon distant wounds. Marino (1931) believes that the effect is due to a trephone, but other work (Gusio and Gibilisco, 1931 Ciantini, 1933) supports Aievoli's claim for hormonal activity

Extracts of testis (many workers) and of ovary favour healing in animals of homologous or even heterologous sex (Lauber 1933 dal Collo 1926). Removal of the ovaries or testis seems to be without effect, though implantation of testis accelerates and grafting of ovary is without effect on healing (Merlini, 1928).

Michail and Vancea (1930) report acceleration with extracts of lachrymal gland. Negative results with spleen tissue are reported by Voronoff and Bostwick (1918) and Aievoli (1923) and Brezovsky's (1930) claims for the thymus are unconvincing.

Nervous influences upon wound healing were related by Lick (1902) to the favourable effect of the hyperaemia following sympathectomy which has been employed in the treatment of indolent ulcers by peri-arterial sympathectomy (Leriche, 1920, 1921 Leriche and Fontaine, 1928). Rieder (1924) agrees that the effect is of therapeutic value in man, but denies any advantage in the healing time of a normal animal.

Aging of the skin

The cause of the atrophy in the skin which accompanies aging is unknown. Disuse atrophy malnutrition, arteriosclerosis, and pressure are all unacceptable,

haemoglobin from red blood-cells (Rollet, quoted by Pack, 1926) in vessels which are paralysed and dilated (Jellinek, 1912). Histologically the cells of the epidermis show a characteristic stretching in a direction perpendicular to the surface of the skin (Freudenthal personal communication)

The epidermis also affords some protection against the weaker chemical irritants and corrosives, though penetration with consequent absorption into the blood-stream is likely to occur along hair follicles and the ducts of glands, even when the epidermis is intact

Foreign bodies introduced through the epidermis accumulate in the dermis to be disposed of by the tissue phagocytic cells As a result, much particulate matter introduced by accident (as in the skin of coal miners) or deliberately (as in tattooing) can be removed. Casper in 1852, observed the complete disappearance of tattoo marks, and fading is well known A recent review of tattoo (Rukstinat, 1941) draws attention to the localization of syphilitic eruptions to the blue portion of the design, though Florange (1909) noted the localization in the red portions, which usually escape owing to the presence of mercury Protection against bacteria and the self-sterilizing action of the skin are discussed in Chapter 8.

Nutrition of the skin

Some evidence, often contradictory exists to show the effect of vitamins and hormones upon the nutrition and repair of normal skin Complete avitaminosis leads to faulty repair and much delay in healing. The effects of the individual vitamins need to be considered separately and the reader is referred to Chapter 4 for information concerning these matters.

Hormones

Disease of the ductless glands gives the following skin changes

ACTION OF HORMONES

Ductless gland	Subcutaneous tissues	Hair	Cutaneous glands	Epidermis
Pituitary				
Acromegaly	Thick skin collagenous hypertrophy	Coarse hypertrichosis	Hyperidrosis Seborrhoea	Epidermal hypertrophy Pigmentation
Cushing's syndrome	Obesity purpura	Hypertrichosis		
Simmond's disease	Obesity			
Thyroid				
Myxoedema	Generalized deposit of myxoedema may be localized		Hypoidrosis	Dry rough, yellow thick Hyperkeratosis Scales
Adrenal				
Addison's disease	Atrophic			Pigmentation

epidermis little water reaches the corium. Some water is imbibed by the keratin, which swells, producing wrinkling and whitish discoloration, well known after prolonged immersion in water. With epidermal injury and inflammation, absorption may be considerable. In a recent review of the subject, Rothman (1943) maintains that the transitional layers between the cornified and non-cornified epithelium are the barriers to absorption. He emphasizes the importance of an electrical double layer in this region due to hydrogen ions on the outside and hydroxyl ions on the inside. The permeability of the frog's skin to ions can be increased by low concentrations of a number of narcotics and decreased by higher concentrations of the same drugs (Hofmann, 1943), but conditions may be exceptional in the frog. Electrophoresis modifies the absorption rate, especially through the skin appendages. In general, lipoid-soluble substances penetrate the epidermis with ease, and Overton's rule, which states that substances penetrate cells in the same relative order as their oil-water partition coefficients (Davson and Danielli, 1943), is usually valid (see also Harry, 1941); amongst these compounds may be mentioned alcohol, phenol, salicylic acid and its esters, resorcin, hydroquinone, lipoid-soluble salts of heavy metals (such as mercuric chloride, lead acetate and oleate, copper) fatty acids, and lipoid-soluble hormones and vitamins and alkaloids, especially nicotine, strychnine, opium or its alkaloids. Mineral fats and oils, especially in liquid form, enter the sebaceous glands and so reach the system (Eller and Wolff, 1940). Lipoid solvents, such as ether and chloroform, enhance the permeability of the skin by disintegrating the lipoid framework of the cells, so altering the physical conditions which impose the barrier to absorption. Male and female sex hormones, for instance, are more easily absorbed percutaneously from ether, benzene, and alcoholic solutions than from lanolin and oil (Moore *et al.*, 1938; Emmens, 1941). The reader is referred to the valuable discussions by Macht (1938), Rothman (1943), and MacKee, Sulzberger, Herrmann, and Baer (1945) for further details.

Most gases, especially oxygen, nitrogen, helium, carbon dioxide, hydrogen cyanide, and sulphuretted hydrogen, are absorbed through the skin. Carbon monoxide, which is insoluble in lipoids, is a notable exception (Bürgi, 1936; Hardy and Soderstrom, 1938; Behnke and Willmon, 1940). Man can take up 0·06–0·66 gramme of oxygen in 24 hours through the skin, but of course this intake is very small in comparison with the respiratory oxygen intake. There is a very real risk of poisoning from absorption of hydrogen cyanide through the skin (Walton and Witherspoon, 1925–6; Fairley *et al.*, 1934).

SKIN GLANDS

The sweat glands

These play an important part in heat regulation of the body (see below). They total 2·15 million, varying from 2,700 per square inch on the palms and soles to 400–600 per square inch on the posterior surface of the neck, back, and buttocks (Krause, 1876). They are rare on the external surface of the pinna and eyelids, and are absent from the anterior surface of the nails, labia minora, internal surface of prepuce, glans, and internal part of the pinna. The largest sweat glands are found on the nipple where they hypertrophy during pregnancy. They are said to be especially well developed in tropical races (Aron, 1911) and poorly developed

and Weldman (1942) speaks of the condition as an example of pure atrophy It may however be significant that light sensitization of the skin by the deposit of haematoporphyrins (Garrod, 1923 Lynch 1934) produces all the characteristic changes of senile skin in a premature form. The resulting disease, xeroderma pigmentosum is hereditary but the relation of its aetiology to that of aging is unknown

In aging skin the main changes are of an atrophic nature, collagen, and elastic fibres fragmenting and disappearing with consequent loss of elasticity The interpapillary processes of the epidermis become flattened, losing a layer of granular cells (Evans *et al.*, 1943) whilst the hair follicles diminish in size or disappear Anomalously the hairs of the beard increase in diameter (Trotter 1922) and the sebaceous glands become hyperplastic. The lowered tolerance to heat is the result of decreased function of the sweat glands.

Fat also tends to disappear from the subcutaneous tissues and is, no doubt, a cause of decreased tolerance of cold in the aged Weidman (1942) comments upon the periodicity of subcutaneous fat in relation to the five ages of life s span infancy is fat puberty and young adulthood are lean middle age is fat, and old age is lean

Other structures may show a hypertrophy or irregular hyperplasia in old age. The horny layer of the skin is often affected by hyperkeratosis, more especially on the exposed parts, and due probably to the effect of light. The blood-vessels often exhibit marked irregular hyperplasia with naevus formation, associated with increase of melanin in the skin A marked irregular hyperplasia may occur in elastic tissue, particularly of the exposed parts (Ejiri, 1936, 1937) Similar changes with subsequent mucoid degeneration produce pedunculated growths of the skin of the neck and upper part of the thorax.

Perhaps related to the changes of aging are differences in the amounts of certain chemical constituents of the skin. The arsenic content of the hair increases with age and is nearly twice as much at 70 years as at 20 years (Brown and Klander 1933). Uric acid increases with age, and may be associated with increased itching (Schamberg and Brown 1923) The mineral content has been studied by Brown (1927) from necropsy material Foetal skin shows a marked capacity to store minerals, but the capacity declines sharply at birth and falls further until the tenth year when the storage capacity rises. The calcium and magnesium content of the skin tend to be parallel, increasing with age, in contrast to the lower values for silicon

EXCHANGE BETWEEN SKIN AND ITS ENVIRONMENT

The skin is a medium for considerable exchange between body water and environment. Even under quiet conditions many grammes of water may be lost daily through this route. Man also loses about 4 litres of carbon dioxide from the skin in 24 hours. Anything which induces skin hyperaemia leads to a sudden rise of carbon dioxide output, whereas ischaemia decreases the output to one-third (Loewy 1926) Penetration of fluids and gases through the skin is very much restricted, partly because of the keratin covering, and the spread of a fatty film over the surface, but also because of the close texture of the cells. With an intact

may be related to the endocrine system. The evidence of a relationship between size and number of sebaceous glands and sex hormone production is confused (Sulzberger Rostenberg, and Sher 1934 Hooker and Pfeiffer 1943 Rony and Zakon, 1943).

Recently an important advance in our knowledge of the function of sebaceous glands seems to have been made. Some fifty years ago Sabouraud (1875) first showed that some forms of ringworm clear up spontaneously with oncoming adolescence. Puberty induced prematurely by administration of theelin and diethylstilboestrol is said to give a similar result (Poth, quoted by Weidman, 1942). Rothman *et al* (1946) now show that with the onset of puberty the sebaceous glands of the scalp excrete high concentrations of low-boiling saturated fatty acids, which possess selective fungistatic and fungicidal action on ringworm fungi. Highly active normal aliphatic monobasic acids with odd numbers of carbon atoms have been isolated from the hair fat of adults. The adult type of hair fat does not kill the fungus spores within the hair but prevents infection of the new hair which replaces the old infected hair after shedding. Such studies may open up a completely new line of investigation of skin function.

The sebaceous glands, like the sweat glands, are probably controlled by special centres in the central nervous system. Secretory nerves no doubt exist, but little is known about them.

TEMPERATURE REGULATION

Foremost among the activities of the living organism is the production of energy for protoplasmic existence is bound up with energy expenditure. The human being derives his energy entirely from the oxidation of foodstuffs, glucose, for instance, liberating 3·8 calories per gramme utilized, fat 9 3 calories, protein 4 1 calories. During such combustion oxygen is consumed to the extent of 1·067 grammes of oxygen for 1 gramme of glucose, 2 876 grammes of oxygen for 1 gramme of fat, whilst 1 gramme of protein uses up 1 382 grammes of oxygen. Water and carbon dioxide are the *chief products of these* exchanges, though the intermediate stages of combustion may be represented in the excretions.

Energy is expended in two ways, first, in performing mechanical work, especially through muscle action, and, secondly in the production of heat. The great source of heat is the muscular system although the liver plays an important part (Hirsch and Rolly 1903 Hirsch and Müller 1903 Senator and Richter 1904). Much of this heat is dissipated, and the mean body temperature is maintained at a remarkably constant level in homoiothermic animals, including man, by a central nervous system regulation of heat production and elimination. It is in connexion with the latter process that we encounter an important function of the skin. Heat is lost through the respiratory passages chiefly by radiation and evaporation, and from the body surface chiefly by radiation and evaporation of water and to a much lesser extent, by conduction and convection. Such mechanisms are largely controlled by temperature and humidity differences in the air and the skin, modified by the extent to which the animal is covered with fur hair or other material of low thermal conductivity and in man by clothing.

in the Fuegians accustomed to extremes of cold The sweat helps to maintain the skin in a supple condition and preserves the acuteness of tactile sensibility Sweating comprises an important adjuvant to urinary excretion assisting in the removal of waste products. The glands excrete substances similar to those in the urine for example chlorides urea, ammonia uric acid, creatinine, phosphates, lactic acid, sulphates, and certain enzymes (Mickelsen and Keys, 1943) They concentrate ammonia Toxic substances are said to appear in sweat and urine in typhoid fever (Stolyhwo 1936) *Antitoxin may be excreted (Neill, 1931)* and under conditions of suppressed urinary output sulphonamides may appear in appreciable quantities in the sweat (Highman 1938) Pigment excretion (chromidrosis) has been described (Way and Memmesheimer 1940) although most dermatologists agree that this is due to bacteria blood has occasionally been recorded, especially with endocrine disturbances

The composition of sweat varies with the region and the duration of sweating, but is not affected by atmospheric conditions and is usually independent of chemical conditions within the body (Adolph 1923) *The levels of sodium chloride in* blood urine, and sweat are not correlated (Lobitz and Osterberg, 1945) Acetylcholine is thought to be the chemical mediator of sweat nerve impulses (Dale and Feldberg, 1934)

Intradermal injection of acetylcholine induces local sweating, woman being much less responsive than man (Kahn and Rothman, 1942)

Special secretory non medullated nerve fibres, with end pieces in contact with the excretory epithelium, have been demonstrated by many investigators, for example, Goltz (1875) and Langley (1891) but special sweat centres in the central nervous system including the spinal cord, have not yet been definitely located, though there is some reason to suspect their existence (Langworthy and Richter 1930 Schwartz, 1937) Sweating is induced by direct excitation of sweat fibres, the stimuli including extreme heat dyspnoea, muscular exercise, or strong emotion (*see below*) The sweat glands of the palms and soles respond most readily to mental stress, even when relatively mild as with mental arithmetic (Kuno 1934a). Hypersecretion involving palms and soles has been noted in stutterers (Greene, 1937)

The sebaceous glands

These are *located on most parts of the body* though the palms and plantar surfaces of the feet are free. New glands can develop in the adult (Ribbert, 1903). Most are closely associated with hair follicles or form a passage for a rudimentary hair but *a few open directly on to the skin surface (Way 1931)* Dark-complexioned persons usually have larger more actively secreting sebaceous glands than blondes (Barber 1922) and Jews are especially liable to seborrhoea. The secretion is a semi fluid substance, sebum *which often forms a thin oily coating on the sur*face of certain areas, especially the nose, forehead, and sternal and scapular regions. The scalp excretes each day an amount of sebum equal to that produced by the rest of the body The daily elimination of *fats by the skin varies between 1 and* 2 grammes (Kuznitzky 1913)

The sebum varies considerably in amount throughout life, being especially copious at puberty and during menstruation and pregnancy so that its production

individual, the surface area of the body and the humidity temperature, and movement of the air. Clothing, of course, modifies these factors.

Two mechanisms exist in the skin whereby water is lost (1) insensible perspiration and (2) sweating. Insensible loss occurs in animals which do not have sweat glands, but also plays a part in man, in whom its demonstration is clear when there is congenital or acquired absence of sweat glands. The literature on the congenital condition is well reviewed by MacKee and Andrews (1924), Weech (1929), Gordon and Jamieson (1931) Lord and Wolfe (1938) de Silva (1939) and Sunderman (1941), whilst Engelhardt and Melvin (1945) discuss acquired anidrosis. The chief features of the disease are absence of sweat glands, and occasionally of lachrymal glands, growth of scanty lanugo hair lack or imperfect development of teeth, and chronic rhinitis. Such subjects show impaired temperature regulation, although water is vaporized normally through the skin and lungs. A somewhat similar acquired condition develops in soldiers training in desert areas (Wolkin, Goodman, and Kelly 1944) The sweat mechanism below the neck may completely fail. Insensible perspiration amounts to 600–700 grammes of water loss in 24 hours. The rate of loss is fairly uniform over the whole body surface except in such regions as the palms of the hands and soles of the feet, where it is most rapid (Burch and Sodeman, 1943), and the trunk, arms, and legs, where it is relatively slow It is still far from certain how the loss takes place. Physical passage of water through the epidermis, probably by diffusion —the rate of diffusion of water through dead skin and loss of water through living skin are virtually the same (Burch and Winsor 1944a and b)—is possible (Kuno 1934b), although escape as water vapour is more likely since the skin is permeable to gases (Martin, 1930) and insensible perspiration is almost devoid of solutes (Benedict, 1915 Hancock, Whitehouse, and Haldane, 1929 Varti, 1932). Physiological control through the circulation of the skin and its vasomotor system modifies these factors (Hardy and Oppel, 1937). Environmental conditions also play their part. When the relative humidity of the air increases, insensible loss decreases, whilst vaporization decreases as the skin temperature falls and increases with temperature elevation (Pinson, 1942). Somewhere around 30° C. water loss from the skin rapidly increases, probably because the sweat glands are called into action (Wiley and Newburgh, 1931) Vaporization from the skin can compensate for diminished loss from the lungs (Adachi and Ito, 1934). Insensible loss is slightly less from the unclothed skin of females than from that of males. The water content of the skin influences such loss, dehydration greater than 6 per cent lowering insensible loss (Adolph, 1933 Newburgh and Johnston, 1934 Hall and McClure, 1936 Winkler *et al.*, 1944) but patients with established oedema appear to have normal insensible losses (Soderstrom and Dubois, 1917 Jores, 1930a Kestermann and Schlenning, 1936). Insensible perspiration is increased 3–10 times in cutaneous lesions in which keratin is overproduced as in psoriasis and exfoliative dermatitis (Fleischer and Rothman, 1945). In ichthyosis vulgaris insensible sweating is practically normal.

When heat production exceeds a certain level or when the temperature gradient between the environment and the body surfaces becomes small insensible perspiration no longer suffices for heat elimination and the sweat glands are brought into action to provide more fluid for evaporation. A human being will vaporize

Heat loss *from radiation has been estimated* at 60–80 per cent of the total loss (Rubner 1902 Dubois, 1937). In the lungs, heat is used up in raising the temperature of inspired air towards the body temperature, and the quantity of heat so lost depends upon the difference between environmental and body temperature, the volume of air respired in a given time and the character of the respirations. A close relation has long been recognized between the blood temperature and the respiratory rate (Goldstein Sihler 1879–1880 Gad and von Mertschinsky) which depends upon nervous controls and hints at a useful arrangement for the organism Skin radiation is in the form of long-wave infra red rays corresponding to a skin temperature of about 32 5° C. at normal body adjustment. Range of radiation begins at a wave-length of about 5μ, extends to 20μ with a peak at about 9μ (Hardy 1934) Such laws as those of Planck (the wave-length depends upon the temperature of the radiating body) Lambert (radiation depends upon profile or *projection* area of the radiating body and not upon total surface), and Newton (amount of radiation is proportional to the area of the surface, the emissivity and *the difference in temperature between the surface and its environment)* are obeyed. The emissivity of the skin is high and almost equals that of lamp black, at any rate for infra red rays in the visible range, however white skin absorbs less energy than dark (Cobet and Bramigk 1924 Hardy 1934) Martin (1930) states that an average blonde skin absorbs only 57 per cent of the heat energy of the noon-day sun in London during summer a Semitic brunette 65 per cent, a Hindu 78 per cent, and a Negro 84 per cent. A tanned skin also absorbs more energy and the heating effect of sunlight is greater than in a fair skin (Dubois, 1937) Apparently the longer waves pass the outer layer of the skin and are absorbed somewhere below this level, especially by melanin. There is evidence that rapid heating of melanin in this region brings sweat glands into action earlier than in non-pigmented regions. *It is difficult to escape from the conclusion that we are dealing here with a set of* compensatory phenomena but many gaps in our knowledge about skin pigmenta*tion still exist (Schultz, 1922 1928 1929 Iljin 1926* Edwards and Duntley 1939 Hamilton 1940) We know very little about regional variations in radiation, although it is obvious that the whole body must be made up of a series of gradients of temperature, and that the ordinary temperature measurement applies only to spots. Further investigations of the flow of radiated heat are urgently required.

Heat is lost through evaporation of water in the respiratory passages and from the skin This implies the changing of water from liquid to gas and depends upon the vapour pressure of the water which is a function of its osmotic pressure. The heat equivalent of water lost as liquid in the secretions and excretions is insignificant (Dubois, 1937) and little heat is expended in bringing food into equilibrium with body temperature On an average, vaporization of water accounts for 24–25 per cent of the *heat loss from the human body (Soderstrom and Dubois,* 1917 Levine and Wilson 1926 1928 Dubois, 1937). The lungs account for about 40 per cent *of the water loss (Benedict and Benedict, 1927)* A gramme of water vaporized from the body surface at room temperature means the loss of about 0 58 large calorie. A man of average size under ordinary basal conditions vaporizes 30 grammes an hour 30 per cent of the skin loss coming from the hands and feet though these include only 12 per cent of the total skin area (Benedict and Wardlaw 1932) Total evaporation depends upon the total metabolism of the

tissues. Convection currents at the body surface are influenced by movements of air by geometrical form and orientation, by movement and by perspiration. (*See* Deighton, 1933 for review.)

With so many factors at work in the complicated business of heat production and heat loss, it is obvious that some sort of regulating mechanism must be concerned if the mean body temperature is to remain constant, as it does in homoiothermic animals such as man and mammals. It is true that most homoiothermic animals are poor at regulating body temperature *at or before birth or even during* infancy but a daily periodic variation of not more than 1.5° C. is seldom exceeded after early childhood (Jürgensen, 1873; Benedict and Snell 1902, 1904). The lowest temperature occurs in the early morning, the highest in the afternoon. There is some variation in temperature, too, at different regions of the skin, especially over protruding and curved parts, over the extremities (which are cooler than *the head and torso*) and *in the* skin covering bones and tendons (Bierman 1936; Burckhardt and Schwammberger 1945).

Experiments show that the region of the corpus striatum is the site of heat control. (*See* Ott, 1914 for early literature, Barbour 1921.) The hypothalamus is especially important, and there is reason to suppose that a centre for reactions to heat resides in the anterior hypothalamus and that one for cold exists in the caudal part of the lateral hypothalamus (Clark, Magoun, and Ranson, 1939). The temperature of the inflowing blood affords the stimulus for bringing into play the thermostat, though the metabolism of the centres may play some part (Serota, 1939). It is surely significant that the hypothalamus is also concerned with regulation of temperature by hormones and by fluid and salt adjustment in the blood. There is close proximity also to vasomotor and respiratory centres. Pathological changes have been described in the hypothalamic region in conditions of hyperthermia (Erickson, 1939; Morgan and Vonderahe, 1939). Minor regulating centres exist in the spinal cord, and it is possible that there is some psychic control of heat regulation (Pembrey 1898; Courtier 1916; Ziegler and Cash, 1938; Gillespie, 1938). Endocrine factors play a part, as witness the disturbed heat regulation associated with adrenal, thyroid, and pituitary lesions. But our synthesis still lacks precision and for the present we can do no more than state the relevant facts.

The factors influencing heat production and heat loss have been well summarized by Dubois in the following fashion.

(1) Heat production is favoured by

(i) higher basal rate, (ii) muscular tensing—cold, emotions, (iii) exercise, (iv) shivering, (v) specific dynamic action of food, (vi) disease

(2) Heat loss is favoured by

(i) cooler environment, (ii) decreased clothing, (iii) increased air movement, (iv) sweating, (v) increased skin circulation, (vi) higher skin temperature, (vii) change in temperature gradient, (viii) increased radiating surface, (ix) panting.

The skin constitutes the barrier between the external environment and the animal's internal economy. It is of vital importance in the preservation of the

about 18 grammes of water per square metre per hour whilst not sweating this increases to 107 per square metre per hour in a room temperature of 40° C. with a humidity of 20 per cent and a skin temperature of 36° C. (Wiley and Newburgh, 1931) The mechanism is well illustrated by reference to the dog, which is singularly inefficient at sweating, and develops fever in hot climates (Dill *et al* 1933). The animal resorts to panting respiration in its attempt at compensation. In the human being, sweat glands are only intermittently in action, especially when there is much muscular activity or the environment is hot. In other words, the sweat glands are called upon when heat elimination by the ordinary methods is not sufficient Thus the nude resting subject under conditions of moderate humidity begins to sweat at about 31 C. but clothing or slight exercise brings sweating on at 25–28° C. (Dubois, 1938 Hardy and Dubois, 1938 Hardy and Soderstrom, 1938) Apparently women have a way of reducing heat production at moderately high temperatures without making use of the sweating mechanism (Hardy *et al*., 1941) As in the case of insensible perspiration sweating is regulated by the blood flow through the skin and here again the vasomotor system with its central control is primarily concerned. A rise of internal temperature alone will induce sweating (Winslow and Gagge, 1941) which points again to a central nervous control Most organs when functioning actively possess an enhanced blood supply and sweat glands appear to be no exception to the rule Sweating leads to the loss of electrolytes such as sodium and chloride, as well as water (Hancock, Whitehouse, and Haldane, 1929 Dill Hall and Edwards, 1938 McCance, 1938a and b) which means that extracellular fluids in the skin are drawn upon in sweat production. As sweating goes on, more sodium and chloride are lost and the subject may suffer from salt depletion but after a time an adaptation response sets in and the salt-content of the sweat decreases though the total amount of sweat is still increased (Robinson *et al*., 1943). However individuals differ in their power of adaptation and some persons are quickly sent into salt depletion others, especially women are highly resistant to this disturbance (McCance, 1938a and b).

Evidence exists that the thyroid hormone is concerned in the control of evaporation Hyperthyroid patients show relatively increased vaporization (Jores, 1930b) but in myxoedema a very small proportion of heat is lost in this way (Gilligan and Edsall 1935) Overactivity of sweat glands is a striking feature of hyperthyroidism. In myxoedema, the presence of a pad of gelatinous fluid in the dermis and subcutaneous tissues quite likely interferes with water exchange through the skin

The other means of heat loss from the skin play a lesser part in temperature control Conduction—the diffuse transfer of heat through solid bodies presenting a temperature difference at their extremities—is not an important factor for human beings (Dubois, 1937) It is modified by temperature gradients in the tissues which in turn depend upon composition by vascularity of surface layers leading to gradient changes (Pickering, 1932) by the nature of the tissues especially the distribution of the insulator fat and by clothing or hair or fur which reduce conduction and convection externally and so modify metabolism. Plucking a goose is said to increase its metabolism by 78 per cent (Giaja, 1929). Convection accounts for 10–12 per cent of the total heat loss in a naked man at rest (Dubois, 1937) It comes into play more especially when there is vasoconstriction in the surface

INFLAMMATION

Penetration of irritants

Penetration of irritants and poisons results in the death of larger or smaller amounts of tissue with liberation of histamine or histamine-like substances, producing a sequence of events grouped together as inflammation. In contrast to histamine, the effect of the histamine-like substance is prolonged, but with neither is there any tendency for cells to migrate from the capillaries into the tissues. Menkin (1940) showed that this is due to a crystallizable, nitrogen-containing body. A polypeptide with similar properties has been isolated from peptic hydrolysates by Cullumbine and Rydon (1946). The sequence of events following injury has been named by Sir Thomas Lewis the triple response, the components of which will be examined as part of the vascular responses of the skin.

Vascular responses

The vascular responses of the skin exhibit a remarkable constancy of type and sequence which were analysed by Sir Thomas Lewis (1927). The white reaction evoked by stroking the skin lightly with a blunt point is interesting as the clinical expression of localized active contraction of capillaries. The contraction is maintained in the face of a venous pressure of 100 millimetres of mercury but the mechanism of its production is doubtful. Vimtrup (1922, 1923) observed constriction of the capillary wall at the points where Rouget cells or their processes encircle them. The Clarks (1925a and b) consider that it is the endothelial cell itself which contracts, and the experiments of Sanders, Ebert, and Florey (1940) suggest that swelling or contraction of the endothelial nucleus may modify the calibre and blood flow of the capillary itself.

Local red reaction

A firm stroke produces the local red reaction due to active dilatation of the end capillary loops. Since it also develops with the circulation at a standstill, the effect of active relaxation of arterioles or venules can be excluded and it develops independently of an intact nerve supply.

The flare

Stronger or repeated stroking produces the second type of red response, the flush or flare, which subsequently involves the skin surrounding the local red reaction. It is the result of arteriolar dilatation and may produce a local rise of temperature of 2° C. or more. This dilatation fills the extensive subpapillary plexuses. There is evidence that the flare is the result of an axon reflex evoked by acetylcholine, though this substance was not demonstrated in the blood draining the site of injury nor in the weal fluid (Rothman and Coon, 1940). Following section of the nerve to the part, the flare persists for 6–10 days (Lewis, 1930; Lewis and Pickering, 1936), or 14 days (Rothman and Coon, 1940), and then disappears. It reappears as regeneration of the nerve is established (Lewis, 1941).

By their action in conserving heat or in dissipating it to the environment, the subpapillary plexuses act as *thermal radiators* (*see above*). Their great extent, estimated by Wollheim (1931) to be capable of storing as much as one-third of the total blood volume, shows their potential importance to the organism in temperature regulation. Protection against cold is afforded by vasoconstriction in which

energy level to which the organism is adapted and at which its activities are carried out most effectively

The importance of these factors in heat balance is shown when we consider fever Fever may be defined as any condition of positive heat balance not due solely to food exercise or environment (Barbour, 1921). A man in whom heat production exceeds heat loss by 230 calories, that is, about 10 per cent of the total heat usually produced in 24 hours, has a fever of 41 C. or 106 F (Dubois, 1937). On the other hand, partial failure of the heat-eliminating mechanism may equally well lead to fever This occurs in infections and neurogenic fever The chief feature of many fevers is increased heat production. As long ago as 1875 Liebermeister found an increase of 21–24 per cent in heat production during the hot stage of a malarial attack, with a 147 per cent increase during the chill. The muscular contractions of the rigor are chiefly responsible for this high figure. The same phenomena occur with intravenous injection of dead typhoid bacilli or other forms of foreign protein (Dubois, 1937) Heat elimination remains practically unchanged for some time after the chill but eventually rises above heat production as the mean body temperature declines. A coincident increase of temperature and heat production is found in typhoid fever (Coleman and Dubois, 1915), but in tuberculosis metabolism is increased by little above normal (McCann and Barr 1920)

When heat elimination fails to keep pace with heat production during a temperature rise the body surface becomes paler and perspiration diminishes. During the stage of increment in many febrile diseases, evaporation from the skin is very low somewhat higher but still below the normal during the fastigium but greatly increased in the stage of decrement (Wassilewsky 1867) Lang (1904) has shown that during fever evaporation from the lungs may be increased whilst that from the skin is decreased or unchanged In pneumonia there is, on the whole, no marked retention of water (Schwenkenbecher 1905 1906, 1907) but in typhoid fever and tuberculosis more solids are excreted than water The rate of blood flow through the arm is much diminished at the onset of fever (Hewlett, 1911).

In fever it is said that the body thermostat is set at a higher level so that a normal temperature is interpreted as cold by the temperature centre, whilst one of 40° C. perhaps feels neutral The skin nerves also seem hypersensitive to cold or hyposensitive to heat (Barbour 1921) These alterations are probably the result of a depressing action of toxins. In support of this view is the observation of Head and Riddoch (1918) that diminished responsiveness of the divided spinal cord occurs in all febrile conditions

In heat stroke, heat retention is due to failure of controlling mechanisms. The skin feels hot and dry and the body temperature rises to 106°–110° F The regulating mechanism does not readily respond to these disturbances and the temperature may remain high for several days. Disturbance of sweating seems to play no important part in causation of heat stroke until mental and physical phenomena become severe (Kuno 1934a and b) Suppression of sweating, either from exhaustion of sweat glands (Hearne, 1919a and b) or due to a paralysing effect of some metabolic product on the sweat glands (Pembrey and Nicol 1898), then appears.

in adults (Okamoto, 1936). In oedema and diabetes, the time is shorter (Seelig, 1931), but it is delayed in intoxication and dehydration.

The exudation which produces wealing, oedema, or blistering persists for a certain time according to the severity of the injury. Ebbecke (1923) showed that dye did not collect in a weal if it was injected into the circulation 5 minutes after the weal had appeared. With more severe injury dye may not reach the site of injury because of local thrombosis. In such injuries it is evident that a time is reached at which permeability returns to normal and exudation ceases. Histological changes throw little light on the problem. In the early states increased stickiness of the endothelium is manifested by carbon particles adhering to the cement substance (Chambers and Zweifach, 1940) from which jets of carbon may be seen to escape at a later stage. Early swelling of endothelium is observed, with mitochondrial changes, ranging from fragmentation and swelling to disappearance (Short, 1943).

That more subtle factors than vasodilatation may be concerned in increasing capillary permeability may be suspected from the observations of Hoff (1927) and Lewis (1927), who reported failure to react to the same injury at a spot previously injured. Escape of dye into the knee-joint of a cat was actually reduced when the sympathetic supply was cut, in spite of thermometric evidence that the blood flow had increased (Engel, 1941).

The triple response is the foundation of the vascular changes associated with inflammation, and it is evoked by a wide variety of physical and chemical injuries. Indeed, it was this variety of cause which suggested to Lewis that the injury acted by local liberation of a diffusible substance. The fact that histamine or a closely related substance evokes the triple response led him to postulate that this substance, or one closely related, was liberated mainly from the injured epidermal cells. In view of the transient effect of the histamine response, contrasting with the relatively prolonged triple response, the diffusible chemical was named the H substance, and by Krogh, the H colloid, suggesting a combination with protein.

Lymphatic reactions in the skin

A rich plexus of lymphatics exists in the subpapillary layer of the corium, which can be studied in the living human subject by the intradermal injection of slowly diffusible dyes. (*See* McMaster 1942, for review.) With such methods it has been shown that lymph flow is increased by application of heat, massage, muscular activity and hyperaemia, and is diminished in limbs that are at rest. Even in a motionless limb lymph flow may be rapid, and it appears that the mechanical effect of the pulse increases the movement of tissue fluid both into and along the lymphatics. A sudden rise in tissue pressure initiates a gradient of pressure which tends to force fluid from the tissues into the lymphatics. In cardiac oedema, however despite the distension of the tissue spaces by fluid and the demonstrable dilatation of the lymphatics, the lymph flow is stagnant and this failure of fluid transport adds to the oedema. In contrast, patients with oedema accompanying renal disease show increased lymph flow in their skin, which is augmented at the onset of diuresis.

Mild stimuli, such as stroking with a blunt instrument, exposure to a temperature of 53° C. for one minute, or to ultra violet light, increase the permeability of

all surface vessels participate. This has been analysed by Sir Thomas Lewis (1941) and others into three types a local persistent contraction, a transient general reaction produced even when the local circulation is cut off and a general persistent reaction which is produced only when the circulation is restored (Pickering, 1932) This mechanism for conserving heat will benefit the organism only if the exposure to cold is not too prolonged. When this happens the mechanism becomes a danger by establishing a vicious circle of vasoconstriction and cooling of the limb, and tissue death may ensue when the temperature of the environment is sufficiently low The vicious circle may be established at higher temperatures than are required to produce necrosis, and prolonged exposure to a temperature of 16 C. will cause the limb to reach that temperature in a majority of subjects (Lewis, 1941) All parts of the body are not equally affected, the most susceptible being the fingers, toes, ears, and nose

The weal

Localized subcutaneous oedema appearing as wealing following more severe local injury is the manifestation of increased permeability of the vessel wall. It is possible to measure the quantity of protein or of dyes, introduced into the circulation which escapes through such damaged endothelium. The rate of lymph flow also increases but a satisfactory index of increase in capillary permeability has not been defined.

The amounts of protein that can be lost from the body in ten days following a severe burn involving 60 per cent of the bodysurface have been estimated by Cuthbertson (personal communication) as follows

Loss of tissue of epidermis – – – –	100 grammes of keratin
" – – – –	551 grammes of collagen
" – – – –	3·4 grammes of elastic
Exudate – – – – – – – –	360 grammes of albumin
" – – – – – – – –	220 grammes of globulin
Katabolic loss of nitrogen equivalent to – –	780 grammes of protein

In less severe cases, localized collections of fluid within or beneath the epidermis constitute a blister The level of separation of the roof is not constant and depends upon the agent employed and possibly upon its power to produce a massive but localized coagulation necrosis of the superficial layers of epidermis. Thus lewisite and thermal burns give a blister roof containing all the elements of the epidermis, separation having occurred cleanly between it and the dermis. Liquid mustard gas, on the other hand results in a ragged separation epidermal cells being left attached to the floor and dermal structures being found still adherent to the roof (Cameron Carleton and Short 1946).

Wealing can be produced in the infant by a variety of agents including the wild nettle (Low 1925) Prausnitz Kustner antibodies of ascaris (Matzinger 1929), histamine phosphate (Carey and Gay 1934) and horse serum (Adelsberger 1927). The results may be variable, for some infants have a greater capacity for wealing than others.

The absorption of weal fluid decreases with age, like quantities being absorbed in half an hour in infancy in one hour at 2 years of age and in an hour and a half

frequency is higher than is the case in the pigeon the rat occupies an intermediate position (Addison and Loeb, 1913 Spain 1915 Spain and Loeb, 1916 Akaiwa 1919). In amphibia, the closure seems to be predominantly the result of amoeboid movement of epithelial cells with insignificant evidence of mitosis (Arey 1932a, b, c). But it must be remembered that the presence in certain species, such as swine and man, of dermal adipose tissue may accelerate healing by projecting fatty tissue into the wound cleft and by providing a smooth floor It may be for this reason that the leaner species (dog, guinea pig, and rabbit) show a greater tendency to produce granulation tissue (Hartwell 1930).

du Noüy (1936) has sought to express the complicated factors involved in cicatrization as a physiological constant referred to the patient's age He found that small wounds cicatrize more rapidly than large and that wounds of the same size cicatrize more rapidly in the young than in the old. A simpler formula by Lemière (1917 1918) shows that the cicatrization time is almost proportional to the greatest width of the wound.

SYSTEMIC EFFECTS OF SKIN DISTURBANCE

Much confusion exists in this type of study and little critical faculty appears to have been exerted in assessing results and separating primary from secondary disturbances. No attempt will be made to review the unsatisfactory literature. We may mention a fairly complete investigation by Babnik (1940) of the chemical changes in the blood of 150 patients with various skin diseases In less than 50 per cent of 19 cases of acute eczema, the blood cholesterol and uric acid were increased and the potassium and non-protein nitrogen were decreased. Slight variations of similar nature were found in 11 cases of chronic eczema. No uniform blood changes were detected in patients with dermatitis, seborrhoea and seborrhoeic eczema, pruritus, and pemphigus, although occasionally the blood cholesterol and uric acid were increased. Babnik concludes that the aetiology of numerous skin diseases cannot be clarified by chemical examination of the blood. When there is considerable loss of fluid from blistering, cutaneous oozing and oedema, as in pemphigus, dehydration and anhydraemia may be pronounced, and abnormal concentrations of sodium, total fixed base, potassium, protein, and non-protein nitrogen are found in the plasma (Talbott, Lever and Consolazio 1940). Extensive burning leads to severe disturbances of similar nature. Such studies have their value in treatment, especially as regards replacement of depleted water and protein stores.

CONCLUSION

(By the Editor)

The sequence of the subjects discussed in this chapter is based on a logical plan, and needs neither elaboration nor explanation. The importance of these subjects does not require comment. Some readers may consider that certain topics demand fuller discussion than they receive but in this the authors scope was limited by the shortage of paper others will be impressed by the number of physiological investigations concerning the skin which have been made in recent years. The increasing awareness of physiologists concerning the importance of

the lymphatic wall This becomes pronounced in the presence of wealing and no *doubt contributes to the* formation and drainage of weals. *Lymphatics are* much more permeable in skin inflamed by injections of toxins or by bacterial products *than in normal skin* and noxious materials have immediate access to the lymphatics *once the* epidermal barrier has been penetrated. However blood infection is *prevented by the* filtering action of the lymph glands into which the skin lymphatics *drain* augmented by the property of antibody formation which such glands possess. *The* investigations of McMaster and his colleagues are important contributions to the dynamic study of one aspect of skin *physiology and should* be studied carefully The new methods might well be applied to *many of the* functional problems of skin disease

Leucocyte migration

The fourth cardinal feature of inflammation migration of leucocytes, is not *evoked by histamine (Grant and Wood, 1928)* nor by the histamine-like substance. *Menkin (1938 1940* and earlier work) has crystallized a nitrogen-containing body leukotaxine tentatively supposed by him to be a polypeptide, which increases *permeability* and promotes cell migration More recently Cullumbine and Rydon (1946) have isolated a polypeptide from peptic hydrolysates, which behaves *similarly* Such compounds, present in damaged tissue, may be compared with others present, for example, in the staphylococcus (McCutcheon and Dixon 1936 *Marchand 1901* and Menkin 1940) which promote leucocytosis.

REGENERATION OF THE SKIN

The *detailed review* by Arey (1936) *has been used in the following* comments upon a few of the many factors involved

The spontaneous arrest of blood flow in a damaged area can occur without thrombosis and is the result of arterial spasm (Kuttner and Barnet, 1920) and of extensive separation of the intima which thus act as a mechanical blockage within the capillary lumen In studies with the skin-capillary microscope, Magnus (1924a and b) observed the arrest of blood flow as the result of contraction and retraction of capillaries, without, however any evidence of thrombosis.

Substances which promote cell growth have been referred by von Gaza (1918) to the effects of ischaemia at the edge of the wound. Such substances promote mitosis (Kornfeld, 1922) The products of cell destruction exert a *stimulating* effect on cultures of granulation tissue (Rix and Greifenstein, 1930) and growth-promoting substances were found by Carrel (1923 1930) in leucocytes and in extracts of the embryo Their chemical nature has been investigated by a number of workers, but with little success.

The invasive properties of regenerating epithelium were studied by Loeb (1898), and Cohnheim noted the atypical hyperplastic appearance of such epithelium It may be as a result of these atypical downgrowths of epithelium that excess connective tissue, including even cartilage, is dissolved and subsequent healing assisted

The rate of epithelialization of a wound is inversely proportional to the size of the wound and shows marked species-differences. In the guinea-pig, the movements of epithelial tongues across the healing surface is more rapid and mitotic

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the skin in the life of the individual is a modern trend which dermatologists will note with satisfaction for we are encompassed by many problems which are likely to be solved only by the skill of those colleagues who work in the physiological laboratories of our universities and medical schools.

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CHAPTER 4

DERMATOLOGY AND NUTRITION

J R MARRACK

PATHOLOGICAL processes in the skin may be due to a variety of factors, among which may be inadequacy of some nutrient in the diet or failure of absorption and abnormal metabolism of this nutrient Treatment with some nutrient may have a beneficial action although it appears to be unrelated to the cause of a disease, as *for example in the treatment of lupus with vitamin D_2 and the prevention of* flea-bites by vitamin B_1 (Eder 1945) The effect of lack of vitamin C on laboratory guinea pigs is remarkably uniform but even among laboratory animals we find that rats although they are used for the assessment of vitamin B_1 in foods, may become independent of an external source of this vitamin Healthy human beings whose diets and conditions of life vary far more than do those of laboratory animals vary still more in their response to lack of any nutrient and to treatment with a nutrient. It is probably due to the multitude of factors involved in producing diseases of the skin and to this variability of response that, while treatment of some skin diseases with vitamins has seemed to have a beneficial effect in a higher proportion of cases than can be ascribed to chance, the effect of such treatment remains uncertain

We are steadily learning more about the functions of various nutrients. We can now estimate the amounts in a diet with a fair degree of accuracy Methods are being evolved by which the further stages in the metabolism and action of nutrients can be studied. These methods are in various stages of development in some, purely technical questions of estimation are unsettled in others the significance of the results obtained is not yet fully worked out. These methods, with recognition of their limitations, should be used and estimates of the amounts of nutrients in the diet should be made in the study of the aetiology of skin diseases that are suspected of being related to nutrition and in assessing the effects of treatment. Such investigations will help to decide what line of treatment may be useful, and the value of such treatment, and will add to our knowledge of the functions of nutrients in the internal economy of human beings.

VITAMIN A

The diseases of the skin caused by deficiency of vitamin A or in some way related to vitamin A, deserve special attention because their study illustrates the ways in which a nutrient may influence the condition of the skin and the difficulties in investigating the nature of the relation between disease and the supply or metabolism of a nutrient.

Detection of deficiency

Diet

In a recent experiment (Accessory Food Factors Committee, 1945) on the effects of deprivation of vitamin A, dark adaptation was slowly restored to normal and concentration of vitamin A in the plasma raised by administration of 1,300 international units (I.U.) of vitamin A per day So far as is known, the pre formed vitamin A in the food is absorbed completely Carotene is transformed into vitamin A but the degree to which carotene is absorbed is incomplete and variable. Although the international unit of vitamin A is defined as the biological equivalent of 0·6 microgram of crystalline β-carotene the actual biological value of β-carotene for human beings is less than the *nominal* value based on the assumption that 0·6 microgram is equivalent to 1 international unit. In the experiment quoted, it was found that 2,600 nominal international units (1,560 micrograms) of carotene in oil would restore dark adaptation but that 1,300 nominal international units were not enough. In the report, *Nutritive Values of War Time Foods* (Accessory Food Factors Committee 1945b), it is suggested that, in calculating the vitamin A value of a mixed diet, the nominal value of the carotene should be divided by 3 (In this publication the international unit of vitamin A is incorrectly defined as the potency of 0·06 microgram of β-carotene it should be 0 6 microgram.) This is important, as pre-formed vitamin A is contained in animal products—milk, butter cheese, eggs, and fish. Vegetables supply carotene only and although figures for the amount of carotene in vegetables or the vitamin A value of vegetables are given in Tables these vary widely from one sample to another

From studies of the amounts required to restore normal dark adaptation after deprivation of vitamin A, the Accessory Food Factors Committee (1945a) conclude that 1,300 I.U of pre-formed vitamin A per day might be considered to be the minimum requirement of an adult to allow a safety margin they suggest that a standard of 2,600 I U of vitamin A (or 5,000 I U of carotene) may be regarded as adequate for the maintenance of normal human beings and as leaving a fair margin for safety This standard agrees well with those based on other experiments (for example those of Booher Callison, and Hewston, 1939 Booher and Callison, 1939), though it is lower than those proposed by the National Research Council of the United States of America.

We may assume that an average daily supply of less than 1,300 I.U per day (calculated as suggested in *Nutritive Values of War Time Foods* (Accessory Food Factors Committee 1945)) is inadequate, even if a large proportion of it is derived from animal foodstuffs further that a daily supply of 2,600 I.U of which a considerable fraction is derived from animal foodstuffs, is adequate for a normal adult (except during lactation and pregnancy) and probably for a child but that, when a large proportion is derived from vegetable sources, an estimated intake of 2,600 I.U or more may be inadequate owing to low content of carotene in the vegetables, deficient absorption or possibly failure of the conversion of carotene to vitamin A.

Specific tests

Vitamin A in plasma.—The result of estimations of vitamin A in plasma are accepted somewhat uncritically Almost all these estimates are based on the

Carr Price reaction. This reaction is not specific the colour formed fades and the rate of fading varies in different sera substances that interfere with the formation of the colour may be present to a varying degree in serum. In practice, estimates made by experienced trustworthy observers may differ by as much as 100 per cent *either way*—that is, the concentration found by observer A may be twice that found by observer B on one occasion while on another observer B may find twice as much as was found by A. Some observers find that the concentration remains approximately constant in the plasma from the same individual taken on different occasions (Kimble, 1939 Yudkin, S., 1941b) while others find considerable variations (Haig and Patek, 1942 Leitner and Moore, 1946) Nevertheless, there is little difference between the average values of the concentrations found in the plasma of normal persons by different observers. This is what might be expected if the estimates of some or all of the observers were liable to random errors in either direction It follows that little significance can be attached to single estimates, for example, those given by Cornbleet, Popper and Steigmann (1944)

The average concentration of vitamin A in the plasma of normal persons is about 120 I U per 100 millilitres. In the Oxford Nutrition Survey values under 70 I U are regarded as low and under 35 I U as very low (as, for example, by Adcock and Fitzgerald 1945) Leitner and Moore (1946) chose 80 I U per 100 millilitres as an arbitrary upper limit of low values. The plasma also contains carotene average normal about 130 I U (or 78 micrograms) per 100 millilitres the low and very low of the Oxford Nutrition Survey being again under 70 and under 35 I U per 100 millilitres (Strictly this should be stated as carotenoids Plasma contains several allied coloured substances estimated together including β-carotene, which is biologically active and lycopene and lutein, which are not *Beta*-carotene makes up about 30 per cent of these substances.)

The concentration of carotene rises and falls in parallel with the intake but vitamin A is stored in the liver and can be mobilized, just as the glycogen of the liver is mobilized to maintain the level of glucose in the blood. Within limits, the concentration of vitamin A in the plasma seems to be characteristic of the individual and little affected by intake. Thus a group of nurses who took 50 000 I U of vitamin A per day for 2 years had no higher concentration in their plasma than did a control group who had no more than was contained in their ordinary diet (Robertson and Morgan 1946) After a large dose of vitamin A, the concentration in the plasma rises to a maximum in about 4 hours, but falls to the initial level in about 24 hours (Ralli Baumann and Roberts, 1941) The concentration rises after a sufficiently large dose of alcohol (Clausen *et al.*, 1940 1941 Hoch 1946) and it may fall to one-half of its previous value when the subject has a cold (Brenner and Roberts, 1943) or fall when the temperature is raised by physical means (Aron *et al.*, 1946) It also falls, after a time, when the amount of vitamin A and carotene in the diet is low but the rate of fall is very variable In the experiment made by Steven (1942) the concentration was appreciably reduced in 9 subjects in 38–87 days, whereas, in the recent experiments quoted above, the concentration was reduced by 25 or more per cent in the plasma of only 4 out of 14 subjects at the end of a year during which their diet contained practically no

vitamin A or biologically active carotenoid 1 subject had as high a concentration at the end of 18 months as at the beginning.

The best index of the state of nutrition in respect of vitamin A should be the amount stored in the liver. According to Popper *et al* (1943) the level in the plasma does not run parallel to the level of the stores in the liver. The concentration, therefore, must be, in part, controlled by unknown factors. Josephs *et al.* (1941) found that low concentrations were more common among badly fed subjects, but suggested that this might be a reflection of the lower concentration of lipoids in their plasma. On the whole, it may be said that the significance of the concentration of vitamin A in plasma (when the estimation is satisfactory) is not fully understood, but that low values indicate either deficiency of vitamin A in the diet or a disturbance of the metabolism of vitamin A.

Dark-adaptation test.—Vitamin A is one of the constituents of visual purple, the pigment in the rods which is involved in vision in a dim light. When this pigment is exposed to light it is broken down and partly destroyed. When the supply of vitamin A is deficient, regeneration of visual purple in the dark, after it has been broken down by exposure to a bright light, is delayed and incomplete. In consequence, adaptation to vision in a dim light is slow and defective. The minimum brightness of an object that can be seen can be measured at intervals in the dark, after a preliminary exposure to a bright light. The minimum brightness or logarithm of the brightness can be plotted as ordinate against the time as abscissa, giving a dark-adaptation curve.

There have been considerable discrepancies between the results obtained in studies of dark adaptation. One reason for these discrepancies is that some investigators measure either the brightness of the light that can be seen by the subject after a few minutes in the dark or the time that elapses before the subject can perceive a test object of fixed brightness. As J Yudkin, Robertson, and S. Yudkin (1943) point out, the shapes of the dark-adaptation curves of different individuals may differ considerably the visual threshold in the early stages of adaptation may bear no relation to the final rod threshold reached after about 30 minutes in the dark, which these authors consider to be the best criterion of dark adaptation in relation to vitamin A. They found that the variations of the final rod threshold from time to time in the same subject were small. If a high final rod threshold falls on treatment with vitamin A, it may be assumed that the impairment of dark adaptation is due to deficiency of vitamin A. It appears that a high final rod threshold, which is lowered by adequate treatment with vitamin A, is the best evidence of deficiency of vitamin A.

However other factors appear to influence the relation of impairment of dark adaptation to deprivation of vitamin A, for in the recent experiment quoted above only 2 out of 14 subjects showed evidence of impairment at the end of 1 year while in Steven's (194.) experiment the threshold (measured in the same way) was raised in 6 out of 9 subjects in from 28 to 87 days.

S Yudkin (1941b) found that the level of the final rod threshold bore no relation to the concentration of vitamin A in the plasma this was confirmed in the recent experiment, except that the threshold rose when the concentration fell below 40 I.U per 100 millilitres In rats it appears that the concentration of

Carr Price reaction This reaction is not specific the colour formed fades and the rate of fading varies in different sera substances that interfere with the formation of the colour may be present to a varying degree in serum. In practice, estimates made by experienced trustworthy observers may differ by as much as 100 per cent *either way*—that is, the concentration found by observer A may be twice that found by observer B on one occasion while on another observer B may find twice as much as was found by A. Some observers find that the concentration remains approximately constant in the plasma from the same individual taken on different occasions (Kimble, 1939 Yudkin S., 1941b) while others find considerable variations (Haig and Patek 1942 Leitner and Moore, 1946) Nevertheless, there is little difference between the average values of the concentrations found in the plasma of normal persons by different observers. This is what might be expected if the estimates of some or all of the observers were liable to random errors in either direction. It follows that little significance can be attached to single estimates, for example, those given by Cornbleet, Popper and Steigmann (1944)

The average concentration of vitamin A in the plasma of normal persons is about 120 I.U per 100 millilitres In the Oxford Nutrition Survey values under 70 I U are regarded as low and under 35 I U as very low (as, for example, by Adcock and Fitzgerald, 1945) Leitner and Moore (1946) chose 80 I U per 100 millilitres as an arbitrary upper limit of low values. The plasma also contains carotene average normal about 130 I U (or 78 micrograms) per 100 millilitres the low and very low of the Oxford Nutrition Survey being again under 70 and under 35 I U per 100 millilitres (Strictly this should be stated as carotenoids Plasma contains several allied coloured substances estimated together including β-carotene, which is biologically active, and lycopene and lutein, which are not. *Beta*-carotene makes up about 30 per cent of these substances.)

The concentration of carotene rises and falls in parallel with the intake but vitamin A is stored in the liver and can be mobilized, just as the glycogen of the liver is mobilized to maintain the level of glucose in the blood Within limits, the concentration of vitamin A in the plasma seems to be characteristic of the individual and little affected by intake. Thus a group of nurses who took 50 000 I.U of vitamin A per day for 2 years had no higher concentration in their plasma than did a control group who had no more than was contained in their ordinary diet (Robertson and Morgan 1946) After a large dose of vitamin A, the concentration in the plasma rises to a maximum in about 4 hours, but falls to the initial level in about 24 hours (Ralli, Baumann, and Roberts, 1941) The concentration rises after a sufficiently large dose of alcohol (Clausen *et al* 1940 1941 Hoch 1946) and it may fall to one-half of its previous value when the subject has a cold (Brenner and Roberts, 1943) or fall when the temperature is raised by physical means (Aron *et al* 1946) It also falls, after a time, when the amount of vitamin A and carotene in the diet is low but the rate of fall is very variable in the experiment made by Steven (1942) the concentration was appreciably reduced in 9 subjects in 38–87 days, whereas, in the recent experiments quoted above, the concentration was reduced by 25 or more per cent in the plasma of only 4 out of 14 subjects at the end of a year during which their diet contained practically no

Diseases of the skin associated with deficiency of vitamin A

de Gouvêa (1883) noticed that Brazilians who had gross night blindness also had dry and rough skins. Bloch (1921) also mentioned the dry skins of children with keratomalacia. In these cases there was no doubt about deficiency of vitamin A, but the diet probably had other defects which may have caused the dryness and roughness but in Mann's experiment (1926) there could be no doubt about the relation to vitamin A. His evidence is particularly good, because all the subjects were living under identical conditions, except that some groups were given extra food and others were not, and full details of the diet are reported. The basic diet, taking the maximum helpings, supplied less than 300 I.U. of vitamin A per day in animal products (milk, cheese fat, and meat) and a nominal 330 I.U. as carotene in vegetables, so that the total actual vitamin A value cannot have been much over 400 I.U. per day—well below any estimate of minimum requirements. Mann reported that the boys eating the basic diet showed a general roughness of the skin, amounting in some cases to minor degrees of ichthyosis. These physical features are no longer observed after a boy has been taking the milk ration (a pint of milk—600 I.U. of vitamin A) for a period of eight or nine months. Of the boys who were given 1¾ ounces of butter (about 1,500 I.U. of vitamin A) it is reported that the skin became softer and of the boys who were given ¼ ounce of watercress (normal value 1,000 I.U.), that there was some improvement in the condition of the skin. No improvement was noted among the boys who were given sugar, casein, or margarine, which contained no vitamin A or carotene. The common factor in three supplements—milk, butter and watercress—which may have caused the improvement was vitamin A as such or as carotene. These boys were between 7 and 11 years old. At this age deficiency of vitamin A may be associated, according to Frazier, Hu and Chu (1943) with general dryness of the skin, but the follicular signs (called follicular keratosis by these authors) are rare. The follicular keratosis seen in older persons and sometimes, according to these authors, in children, consists of firm papules, usually 2–4 millimetres in diameter which appear particularly on the antero-lateral aspects of the thighs, the postero-lateral aspects of the upper arms, the calves, and the back of the shoulders. The follicles have a keratinized plug which projects as a horny spine; they may have a pigmented areola. A broken hair may project from the follicle, or a coiled-up hair may be released when the plug is removed. Stress is laid on the presence of the horny spine: the skin is said to feel like a nutmeg-grater. However, according to Nicholls (1933) and Fasal (1944) the papules may finally become large and flat hence the name, phrynoderma (toadskin), which would be most unsuitable for lesions of the nutmeg-grater type. Usually the skin is dry and scaly. There is progressive thickening of the epidermis as the follicle is approached. The layers of keratinized epithelial cells in the outer ends of the follicles are thickened, and the outer part of the follicle is filled by a plug consisting of concentric layers of keratinized material surrounding the broken or distorted hair. The sebaceous glands may be atrophied or destroyed. The excessive formation of keratinized epithelium may be regarded as an example of disturbance of the formation of epithelium, such as occurs in animals deprived of vitamin A.

A comparable follicular lesion has seldom been produced in experiments. The changes in the skin described in early experiments on rats were apparently

vitamin A in the retina is maintained when the concentration in the plasma falls. There must, therefore, be a mechanism to control the transfer from plasma to retina.

When they occur xerophthalmia and keratomalacia are evidence of severe deficiency of vitamin A These severe lesions are very rare in Great Britain to-day Kruse (1940 1941) described changes in the sub-epithelial tissues of the anterior surface of the eye, which they considered to be evidence of deficiency Kodicek and Yudkin (1942) considered that examination of the epithelial layer would be more likely to detect changes due to deficiency of vitamin A Robertson and Morgan (1946) found thickenings, as described by Kruse, among nurses who were getting an average of 4 000 I U of vitamin A from animal products per day in their diet, besides considerable amounts of carotene The thickening did not improve in 20 of these nurses who took an extra 50 000 I U of vitamin A for 2 years the changes in the eyes of these 20 during the 2 years were similar to the changes in the eyes of 20 who took no extra vitamin A The presence or absence of these changes is of no significance in diagnosis.

Keratinizing metaplasia

One of the cardinal changes that are seen in animals deprived of vitamin A is keratinizing metaplasia of epithelia. The epithelium in for example, the cornea the bronchioles or the pelvis of the kidney is replaced by a stratified keratinized epithelium The change is reversible when the animals are treated with vitamin A fresh epithelial cells are formed that have the structure and functions of the original epithelial cells

In experiments on rats, made by McCullough and Dalldorf (1937), true keratinizing metaplasia was not produced by irritation unless the rats were deprived of vitamin A but these experiments are not enough to show that irritation or inflammation will never cause this type of metaplasia in rats that are fed adequately As keratinized epithelium is formed in certain sites in animals that receive abundant vitamin A we may suppose that vitamin A is one of the balancing factors that control the development of epithelium, and that a change towards the formation of keratinized epithelium may result from deficiency of vitamin A or from excessive action of other factors.

Keratinizing metaplasia in human beings has been attributed by those interested in problems of nutrition (for example, Blackfan and Wolbach 1933) primarily to deficiency of vitamin A in some instances the evidence of this deficiency has not been convincing. On the other hand morbid anatomists commonly hold that this metaplasia is produced by irritation or inflammation. It seems that there have been no adequate investigations concerning the evidence of this type of metaplasia in subjects not suspected of deficiency

Much remains to be learned about the metabolism of vitamin A—its absorption, transfer from plasma to tissues and its utilization its storage and mobilization its [illegible] or mode of action in cells. At present we find ourselves in disagreement about estimates of the concentration of vitamin A in plasma and of the state of dark adaptation

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A comparable follicular lesion has seldom been produced in experiments. The changes in the skin described in early experiments on rats were apparently

non-specific and due to defects in the diets other than lack of vitamin A. Hyper keratosis of the pilo-sebaceous follicles, comparable with that seen in human beings, has been produced by Moult (1943) by feeding rats on a diet that contained insufficient vitamin A the degree of hyperkeratosis varied inversely with the amount of vitamin A with which the rats were supplied In experiments in which human beings have lived for considerable periods on diets that contained minimal amounts of vitamin A, as such or as carotene, this follicular hyperkeratosis has been noted in one instance only after 190 days After treatment with 80 000 I U of vitamin A for 17 days, the skin appeared to be normal but there were still plugs in the follicles (Steffens, Bair and Sheard, 1939) In the recent experiment mentioned above, no difference was found, in the incidence and severity of enlargements of their hair follicles, between the group deprived of vitamin A and a control group.

The evidence that this dermatitis is due to deficiency of vitamin A, particularly in the cases seen in Asia and Africa, seems convincing. The patients diet contained but little vitamin A mainly in the form of carotene. In Malaya, Fasal (1944) saw no cases among Chinese, who ate a varied diet including vegetables and fish among Tamil children who ate few green vegetables, the incidence was 25·6 per cent, whereas among Malay children who ate large amounts of green vegetables, the incidence was only 2 per cent. Other signs of deficiency of vitamin A were found Among the original cases of Frazier and Hu (1931) the diagnosis of deficiency was based on the presence of keratomalacia. Loewenthal (1933) found 45 cases of xerophthalmia 71 cases of night blindness, and 75 cases of this dermatosis among 81 cases of deficiencies so that of the 75 cases of dermatosis at least 39 must have had xerophthalmia and 65 must have been night blind. McKenzie (1939) noted the occurrence of outbreaks of night blindness on estates in Tanganyika Territory where some 50 per cent of hospital patients had follicular keratosis, and found that the concentration of vitamin A in the liver was low The malady disappeared when suitable treatment was given such as cod liver oil (Loewenthal, 1933) other preparations of vitamin A (which may contain vitamin D as well), carotene (Frazier and Li 1938) or red-palm oil (Fasal 1944) Fasal claimed that the lesions were cured by the local application of red palm oil. If the action were due to action of vitamin A, this would involve the absorption of carotene through the skin for conversion to vitamin A in the liver as the improvement was not confined to areas treated by local application, it appears that this must have happened.

Recently Stannus (1945a) has suggested that the dermatosis supposedly due to vitamin A deficiency has no specific relationship to vitamin A deficiency he appears to doubt the evidence of the relation of the conditions described (for example by Frazier by Loewenthal and by Fasal) to deficiency of vitamin A. In the nutritional surveys made for the Ministry of Health by teams of which Dr Stannus was a member one of the supposed signs of malnutrition looked for and recorded was folliculosis Among school-children of 11–16 years of age the incidence was about 15–20 per cent in boys and 20–23 per cent in girls exceptionally figures of 50 per cent of boys and 80 per cent of girls have been noted. Stannus (1945 a and b) writes of this condition as follicular keratosis, gives a description of the histology similar to that of the dermatosis of for example, Frazier and Hu (1931) and appears to regard the two conditions as identical. It

could hardly be maintained that 20–35 per cent of girls in Great Britain have a dermatosis like those illustrated by Frazier *et al* (1931 1936, 1943), Fasal (1944) or Platt (1945) (see Fig. 1). Frazier *et al* (1943) write as follows

> It is also difficult to judge how frequently keratosis pilaris was included as a sign of vitamin A deficiency We have never included instances of this minor but widely prevalent lesion among the cases of vitamin A deficiency that we have reported. It is doubtful whether there is evidence to indicate its relation to a nutritional disease. Scattered lesions of mild keratosis of hair follicles or the thighs and buttocks from which the removal of a superficial keratinous plug releases a coiled hair are so frequent, especially in persons who bathe but rarely and some of more hygienic habits, that one hesitates to draw general conclusions as to their etiological significance. Furthermore, it does not seem necessary to think that all forms of keratosis of the hair follicle are related to a deficiency of vitamin A.

In some of the cases in which the dermatosis is ascribed to deficiency of vitamin A, the evidence of deficiency is not wholly satisfactory Lehmann and Rapaport (1940) found that some of the children who had a dermatoses of this type were getting moderate amounts of vitamin A in their food they considered that the dark adaptation was subnormal, but were using the method of Jeans, Blanchard, and Zentmire (1937), in which readings are made in the early stages of adaptation, and their significance, therefore, is doubtful. This method was also used by Jeghers (1937), who found cases of the dermatosis amongst American medical students.

Deficiency of vitamin A in Great Britain is not out of the question. Adults, when they are allowed only 2 pints of milk a week, should get about 1,000 I U per day from animal sources, and school-children, who can get 5 pints of milk a week, should get about 1,300 Many do not get their full allowance, and a fair helping (3½ ounces) of the favourite green vegetable, cabbage, supplies only a nominal 900 I.U (actual value nearer 300 I U). However experiments were made in Salford and Stoke-on-Trent (Bransby *et al.*, 1946), in which children were given 4,000 I U of vitamin A and 50 milligrams of ascorbic acid with other vitamins and calcium salts. No difference was found in the incidence of the folliculosis of the teams of the Ministry of Health between these children and control groups of children. McIntosh, *et al* (1946) estimated the vitamin A in the plasma of boys at a training school, among whom 29 per cent had been found to have folliculosis Of this condition they wrote that it is said to be an earlier stage of follicular keratosis, which is regarded by many writers as a manifestation of avitaminosis A Some remarkably low concentrations were found, although in a survey the amount of vitamin A in the boys diet appeared fairly satisfactory (Cook *et al.*, 1944). No relation was found between the incidence of folliculosis and the level of vitamin A or ascorbic acid in the plasma. Administration of vitamin A (13,500–27,000 I U per day) had no effect on the skin lesions.

The question arises whether the lesions seen in vitamin A deficiency and the follicular condition as seen in Great Britain differ in kind or in degree only It seems to be reasonable to suppose that there is no essential difference and that this hyperkeratosis of the pilo-sebaceous follicles may be caused by a number of factors.

A similar dermatosis is seen in scurvy although among Serbian troops it was most common on the anterior and inner aspects of the thighs, and the follicles of

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treatment and was normal after In 8 out of 10 cases the concentration of vitamin A in the plasma was low (normal limits by the method used are given in the second paper) (Peck *et al* 1943a) In 1 case the concentration did not rise on treatment and in 2 cases it fell rapidly below the normal range when treatment was stopped. All of the 4 cases of Carleton and Steven (1943) had normal dark adaptation. After treatment was stopped the concentration of vitamin A in plasma was low in 1 case but normal in 2 others. In the remaining case the concentration was normal during treatment. The average concentration in the plasma was low in 3 of the 6 cases investigated by Leitner and Moore (1946) and fell at times to very low levels, but rose on treatment with vitamin A In the other 3 cases the average concentration was normal.

In 6 of the 7 cases of Porter Godding, and Brunauer (1946) the final rod threshold was measured by the method of S. Yudkin (1941a). In 3 it was slightly subnormal and in 2 subnormal It was not changed significantly by treatment with large doses of vitamin A. In 2 out of 4 cases tested, the concentration of vitamin A in the plasma, before treatment, was slightly low (52 and 69 I.U per 100 millilitres) by the method used the concentration in the plasma of 19 nurses ranged from 105 to 134 with an average of 134 I.U per 100 millilitres (Hoch, unpublished). In all the 5 cases tested after treatment the concentration was over 100 I.U per 100 millilitres. Cornbleet, Popper and Steigmann (1944) found a normal concentration in the plasma of 1 case.

It may be said that, in these 28 cases quoted above, evidence of vitamin A deficiency is found in a larger number than might be expected as a matter of chance. The most striking abnormality is the failure of the concentration of vitamin A in the plasma to rise on treatment with vitamin A in large doses, and its rapid fall when treatment is stopped (Peck *et al* 1943 a and b) but the response to treatment seemed to have no relation to the presence or absence of evidence of such a disturbance.

Pityriasis rubra pilaris

Improvement after treatment with vitamin A has been reported in this disease (see Leitner and Moore, 1946). In 3 cases, Brunsting and Sheard (1941) found that the dark adaptation was definitely subnormal. In these cases the full adaptation curve was traced up to 20 minutes the final rod threshold was lowered on treatment with vitamin A.

Curtis (1943) reported that the concentration of vitamin A in the plasma in 3 cases was about one-half the normal. Cornbleet, Popper and Steigmann (1944), and Leitner and Moore (1946) found a low concentration in 1 out of 2 cases. Weiner and Levin (1943) reported that the dark adaptation was low in 5 patients and did not rise on treatment with vitamin A but the method used was that of Jeans, Blanchard, and Zentmire (1937), with readings after 10 minutes in the dark, and the results are untrustworthy Porter and Godding (1945b) found a high final threshold in 1 case the threshold was lowered in treatment with vitamin A, though not to the normal level and rose again when treatment was stopped.

These two diseases are not cured by treatment with massive doses of vitamin A. Some abnormality of the skin usually remains, and relapses occur when treatment is stopped. In many cases no evidence of disturbance of metabolism is found

pubic hairs were affected in 20 per cent of cases (Wiltshire 1919). Again, small hyperkeratotic papules appeared over the buttocks and posterior aspects of the calves of an experimental subject who had lived on a diet devoid of ascorbic acid for 134 days but had taken 30 000 I U of vitamin A per day the skin also became dry In a further 3 weeks the dermatosis became worse and was considered to resemble a mild form of that due to deficiency of vitamin A When 1 gramme of ascorbic acid was given daily without any other alteration of the diet the dermatosis cleared up (Crandon Lund and Dill 1940) Sullivan and Evans (1945) consider that the development of hyperkeratinization of hair follicles in rats deprived of vitamin A may be delayed if abundant vitamins of the B complex are supplied and Fasal (1944) found that some cases do not improve unless the protein intake is increased and vitamins of the B complex are added. Friction or pressure contributes to the appearance of visible papules Rao (1937) found that the histological changes might be seen in follicles of the skin of patients with keratomalacia who had no follicular eruption The papules commonly appear on sites where clothes rub and hairs are broken off—the extensor and outer surfaces of the upper arms and thigh and in Malaya on the shoulders and buttocks. Among Tamil women in Malaya the earliest lesions occur on the left elbow and left thigh above the knee, because they rest the left elbow on the knee when weeding (Fasal, 1944)

It is reasonable to suppose that the transfer of vitamin A to the skin like the transfer to the retina is controlled by some mechanism The balance of factors that control the development of epithelium may be upset by deficiency of vitamin A, by a fault of this mechanism of transfer or by other factors, such as friction, unrelated to vitamin A When hyperkeratosis is primarily due to deficiency of vitamin A treatment with vitamin A not necessarily in large doses, should cure the condition When the balance is upset by difficulty of transfer or some unrelated factor it may be restored and the skin defect cured by large doses of vitamin A.

Darier s disease and pityriasis rubra pilaris

In Darier s disease and in pityriasis rubra pilaris a hyperkeratosis of the pilosebaceous follicles occurs which is similar to that of the keratosis follicularis that is associated with deficiency of vitamin A.

Darier s disease

Treatment with large doses of vitamin A has been tried in a considerable number of cases Leitner and Moore (1946) and Porter Godding and Brunauer (1946) give a series of cases reported in the literature, apart from their own cases. With regard to the clinical aspects, all that need be said here is that the number of cases that improved after treatment with large doses of vitamin A seems to be greater than might be expected to occur spontaneously The dark adaptation and the concentration of vitamin A in the plasma have been used as evidences of the state of supply or of metabolism of vitamin A

In the series of Peck *et al* (1941 1943b) the dark adaptation was tested by Hecht the full adaptation curve of the cases is illustrated. In 1 case the adaptation was subnormal after only 11 days of treatment with vitamin A, in which time a return to normal could not be expected In 1 case the adaptation was subnormal before and just within normal limits after treatment in 2 cases adaptation was not tested before

pyridoxin (vitamin B_6, adermin), pantothenic acid (filtrate factor), biotin (anti-egg-white factor vitamin H), folic acid, p-amino-benzoic acid (anti-grey-hair factor). There is some justification for including these vitamins in a group as several are members of enzyme systems for example riboflavin and nicotinamide take part in the same chain of reactions in the oxidation of glucose.

Niacine

The substance that is active in the body is nicotinic acid amide (nicotinamide) and this can be synthesized in the body from nicotinic acid. It is convenient to use the word *niacine* to include both substances. In our pre war diet nearly two-thirds of the niacine came from meat. White flour contains considerably less than does flour of higher degrees of extraction. After 85 per cent extraction became compulsory in the spring of 1942, the increase in the niacine in flour compensated for the decrease due to lower consumption of meat. There was a slight fall in 1945, when the degree of extraction was reduced to 82½ and, later to 80 per cent.

However human beings seem not to be wholly dependent upon their food for their supply of niacine, but to have an accessory source in that synthesized by micro-organisms in their intestines. The evidence for this is based on studies of the products of the metabolism of niacine. The chief end-product of niacine is N-methyl-nicotinamide—also called nicotinamide-methochloride. The amount excreted in the urine may be considerably more than can be accounted for by the niacine in the food (Ellinger and Coulson 1944). Both normal subjects and persons with pellagra excrete considerably less after administration of succinyl-sulphathiazole by the mouth (Ellinger Coulson and Benesch, 1944 Ellinger Benesch, and Kay 1945) which inhibits the growth of susceptible micro-organisms in the intestine and, in consequence, stops the synthesis of nicotinic acid by them. Sulphathiazole, given by mouth, which has little effect on micro-organisms in the intestine, and succinylsulphathiazole, injected parenterally do not reduce the amount of the end-product excreted. It is inferred that niacine is synthesized by micro-organisms in the intestine and that a considerable amount of this is absorbed.

It appears from experiments that the substrate from which niacine is synthesized is tryptophane (Rosen, Huff and Pertzweig, 1946). The bacterial flora of the intestine is influenced by the nature of the food. We now seem to have an explanation of the association of pellagra with maize, which contains little less niacine than do other grains and of the efficacy of milk, which contains little niacine in preventing pellagra. The theory whereby pellagra was ascribed to lack of first class protein (as advanced by Wilson in 1921) seems to have been not wholly incorrect.

Ellinger Benesch, and Kay (1945) also found evidence that the ability to absorb niacine was impaired in pellagrins.

There are three reasons why a person may not obtain sufficient niacine.

(1) Impaired absorption of the vitamin.

(2) Inhibition of the appropriate micro-organisms by antibiotic drugs.

(3) Defects in the food which may contain little niacine, fail to stimulate the growth of micro-organisms that synthesize niacine, or contain too little of the substrate from which niacine is synthesized.

but the frequency of such disturbances among the patients is higher than among normal persons or among those suffering from a number of diseases of the skin (Porter and Godding, 1945a Leitner and Moore 1946) This high incidence is in accord with the supposition that an abnormality of the metabolism of vitamin A can render the cells of the skin more susceptible to disturbance of their development by the primary causes of the disease, whatever they may be but there is no reason to suppose that the defect in the metabolism of vitamin A is the primary cause of the disease. In a case of keratosis blenorrhagica (for example) Combes and Behrman (1942) found that treatment with large doses of vitamin A was followed by rapid improvement after other treatments had proved to be ineffective In this instance deficiency of vitamin A cannot have been the primary cause As was suggested in relation to keratosis follicularis, the balance of factors controlling the development of epithelium may be upset by deficiency of vitamin A, by disturbance of the metabolism of vitamin A or by unrelated factors.

In all cases in which the patients have been benefited by treatment with vitamin A the doses used have been many times the normal requirements this would be expected if the effect of the vitamin were to restore the balance between factors influencing the development of cells The metabolism of vitamin A in these diseases should be investigated as fully as is possible. Until more is known about the metabolism of vitamin A its use in treatment of these diseases must remain empirical

Ichthyosis

The occurrence of dryness of the skin in patients suffering from deficiency of vitamin A has led to investigation of the metabolism of vitamin A in patients suffering from ichthyosis and to the trial of vitamin A as treatment Rapaport Herman and Lehmann (1942) reported improvement in 5 cases and quote from the literature other examples of improvement in these cases In 1 case, reported by Vogel (1940) the dark adaptation was subnormal and improved on treatment with vitamin A but these measurements of the degree of adaptation were made with the biophotometer after only 10 minutes in the dark. Peck Glick, and Chargin (1943a) found both the final rod threshold and the concentration of vitamin A in the plasma to be low in 2 cases nevertheless, in these cases treatment with vitamin A did not improve the condition Leitner and Moore (1946) found somewhat low concentrations of vitamin A in 2 out of 3 cases There is, therefore, some evidence of disturbance of the metabolism of vitamin A in this disease.

THE VITAMIN B COMPLEX

In the early stages of their study vitamins were divided into fat soluble A and water-soluble B It was soon realized that other water-soluble vitamins, besides the antineuritic factor (vitamin B_1 aneurin or in America thiamine) which was first recognized were present in yeast and in liver extracts These were called by a variety of letters and names. A large number but not necessarily all, have been sorted out and analysed A full account is given in the *Proceedings of the Nutrition Society* (1946) (vol. 4 pp 79–154) The group included nicotinic acid and nicotinamide (P P factor anti pellagra factor) riboflavin (vitamin B_2, vitamin G)

Milk, adults	2 pints per week	–	0·27 milligram riboflavin per day
Milk, school-children	5 „ „	–	0·61 „
Cheese	3 ounces per week	–	0·06 „
Meat	16	–	0·16 „ „ „
Flour (85 per cent extraction)	6·3 ounces per day	–	0·53 „ „

Beer contains about 0·28 milligram per pint. Other foodstuffs (except the fats) contain small amounts of riboflavin which add up to complete a total of 1·5–2 milligrams. A person who drinks little milk or beer may well take less than 1 milligram of riboflavin per day. It might be expected that signs of deficiency would not be uncommon in Great Britain.

Ariboflavinosis

The skin lesions that are considered to be typical of riboflavin deficiency are as follows.

Angular stomatitis, beginning with pallor at the corners of the mouth, followed by maceration and transverse fissures. The lesions remain moist and become covered with a honey-coloured crust.

Cheilosis, characterized by denudation of the epithelium of the vermilion border of the lips.

Skin eruptions.—A fine, scaly slightly greasy desquamation on a slightly erythematous base in the naso-labial fold, on the alae nasi, in the vestibule of the nose, and on the ears. Fine filiform lesions, on a greasy base, due to the formation of sebaceous plugs in the follicles, may be noted, especially at the base of the alae nasi and also on the forehead.

The term, cheilosis, is often used to include angular stomatitis. Stannus (1944) points out that, according to the derivation of the word, it should be used for lesions of the lips only. He objects to the use of perlèche to designate angular stomatitis, considering that, from its history the word may denote an impetiginous lesion. Actually (Riddle, Spies, and Hudson, 1940) this lesion at the angles of the mouth in ariboflavinosis yields *Staphylococcus aureus* in pure culture in 80 per cent of cases and *Streptococcus haemolyticus* in 20 per cent; the bacteria disappear when the lesions heal after treatment with riboflavin.

Jolliffe *et al* (1939) and Spies *et al* (1939b) have described filiform lesions, on a greasy base, which may occur on the forehead, ears, and other parts of the body as well as in the alae nasi and the naso-labial folds. This condition (which appears to be the same as the dyssebacia of Smith, Smith, and Callaway (1941) mentioned below) was not improved by treatment with nicotinic acid, but responded to treatment with riboflavin or with preparations of liver and yeast.

Other lesions, attributed to deficiency of riboflavin, which might be considered in diagnosis, include glossitis, characterized by a clean tongue of a purplish-red colour having hypertrophic, flattened, mushroom-shaped papillae and invasion of the conjunctiva of the cornea by loops of capillaries visible with the slit-lamp microscope. There has been much discussion of the diagnostic value of the last sign (Kodicek and Yudkin, 1942; Gregory, 1943; Ferguson, 1944). It is generally agreed that increased vascularization around the limbus, without invasion of the cornea by loops of capillaries, cannot be regarded as a sign of riboflavin deficiency. Spies *et al* (1945), who discuss the occurrence of ocular disturbances, consider that not one of the lesions described is pathognomonic of riboflavin deficiency.

Pellagra

Pellagra with or without the typical skin lesions, may occur in Great Britain among people eating a monotonous and inadequate diet.

Deficiency of niacine, with skin lesions, may follow treatment with the sulphonamide drugs which are used for disinfection of the intestine (Hardwick, 1946) a case has recently been described which followed treatment with penicillin, given by the mouth. In this last case deficiency of niacine was demonstrated, first by the low excretion of nicotinamide methochloride and secondly by the slight rise in the excretion after doses of nicotinamide. The synthesis of niacine in the intestine of this patient may have been abnormally low as she had had 3 attacks, before those provoked by penicillin, when eating a diet containing little meat.

The amounts of nicotinamide-methochloride excreted in the basal state and after a dose of nicotinamide appear to be satisfactory indices of the state of nutrition with respect to niacine, and the estimations should be used in diagnosis in cases suspected of niacine deficiency

Pellagrins are prone to be deficient in other vitamins, besides niacine, and may not recover until these are supplied Spies, Bean and Ashe (1939a) have reported cases in which the patient did not recover when treated with vitamin B_1 riboflavin and niacine, but responded to a single dose of pyridoxine Wright, Samitz, and Brown (1943) found that some cases were improved promptly by 1 dose of pyridoxine, while others were not affected

Moore, Spies, and Cooper (1942) have found that the skin of pellagrins is abnormal in areas not affected by the rash. We have, therefore in this disease also two factors that combine to produce the clinical lesion of the skin first the deficiency of a vitamin which in this case is the primary cause of the malady and secondly the effects of sunshine, pressure or rubbing, which are secondary aetiological factors.

Riboflavin

In the early experiments on human beings (Sebrell and Butler 1939) the lesions regarded as characteristic of riboflavin deficiency improved when 0·025 milligram of riboflavin per kilogram of body weight was given daily in 9 out of 10 subjects the improvement was rapid in 1 of these subjects the improvement was slow until the dose was increased to 0·05 milligram per kilogram each day It may be concluded that as a general rule, about 1 5 milligrams will be sufficient for the day's requirement Personnel of the Royal Air Force, getting from 1 5 to 2·6 milligrams per day with an average of 1·9 milligrams (Macrae, Barton Wright, and Copping 1944) showed no signs of riboflavin deficiency (Lyle, Macrae and Gardiner 1944) An outbreak of signs of riboflavin deficiency has been reported among troops whose daily intake of riboflavin had fallen from about 1·6 milligrams to about 1·0 milligram per day the outbreak ceased when improvements in the diet raised the intake again (Jones *et al* 1944).

The chief source of riboflavin in the food is milk. The amounts supplied by the chief foodstuffs, in the quantities obtainable at present enforced in England under the food rationing scheme, are as follows

cheilosis and pellagrous lesions has been mentioned already. Wright (1942) has seen rapid improvement of seborrhoeic eczemas on treatment with 50 milligrams of pyridoxine per week. Pyridoxine therefore may be one of the more active substances in liver and yeast.

Good results have been claimed to follow the treatment of acne with injections of liver extracts (Marshall, 1939; Stokes and Strenberg, 1939). Jolliffe *et al* (1942) selected 2 groups of students with acne: 1 group was treated with 20 milligrams per day of pyridoxine, while the other was not. Of the pyridoxine group nearly 25 per cent were cured and 57 per cent improved, whereas, of the control group, none was cured and only 20 per cent were improved. The most remarkable point in this report was the short time that elapsed before improvement was detected.

The state of nutrition with respect to pyridoxine can be measured by estimating the amount excreted in the urine after a test dose (Spies *et al.* 1940), but this test has been even less used than has the similar test with riboflavin. If it is found to be satisfactory on further trial, it should prove to be useful in the study of seborrhoeic conditions.

Biotin.—In rats that are fed with large quantities of raw egg-white, a characteristic dermatitis develops, and they lose weight and become partially paralysed. The egg white contains a protein called avidin, which combines with biotin, prevents its absorption and so leads to biotin deficiency.

> Sydenstricker and his colleagues (1942) fed 4 human subjects on a basic diet free from vitamins of the B group, which included large amounts of dessicated egg-white. Supplements of vitamins of the B group were given; these included pantothenic acid and pyridoxine, but not biotin. In 7–8 weeks the skin of all the subjects became grey and pale and in 9–10 weeks dry with a fine branny desquamation. The concentration of haemoglobin and the number of red corpuscles in the blood fell, and the patients complained of symptoms resembling those of deficiency of vitamin B_1. When biotin was injected the symptoms were relieved in 3–5 weeks and the pallor and dryness of the skin in 4 weeks. The minimum effective daily dose appeared to be 0.15 milligram of a biotin concentrate.

Few people in Great Britain can indulge in such excessive egg eating, but the minimum dose required to cure the disease is larger than the amount contained in ordinary diets (35–60 micrograms per day). Deficiency of biotin may contribute towards causing skin disease when the diet does not supply a sufficiency of other vitamins in the B group.

Synthesis in the gastro-intestinal tract

Micro-organisms in the rumen of ruminants synthesize large amounts of vitamins of the B group; in consequence these animals are not dependent upon their food for the supply of these vitamins (although they must get their supply of vitamins A and D from their food). Among non-ruminants it was first found that rats could sometimes remain in health although their food contained no vitamin B_1. This occurred particularly when the rats were fed with raw potato starch. It appears that a considerable proportion of the starch passes through the intestine undigested, and that this favours both the formation of vitamin B_1 by micro-organisms in the intestine and the absorption of this vitamin. In the ordinary way, although vitamin B is formed in the intestine, it is not absorbed. This formation and absorption of vitamin B_1 in the bowel is called *refection*.

Tests of deficiency

The state of nutrition with respect to riboflavin can be tested by measuring the amount excreted after a test dose of 10 milligrams (Melnick *et al* 1945) but this test is not yet widely used and further investigation of the significance of the results is needed.

The greater part of the cases of typical skin lesions which have been cured on treatment with riboflavin have been in the United States of America for example those recorded by Spies *et al* (1940) Cases in Great Britain and Northern Ireland have been reported by Duckworth (1942) and Deeny (1942) D C. Wilson (1941) found a child who was having a pint of milk a day (0 85 milligram of riboflavin) but had angular stomatitis the stomatitis was cured when the child was given 20 milligrams of riboflavin in 23 days. In surveys in Great Britain cheilosis and angular stomatitis have been found in 2 or 3 per cent of the subjects.

If the function of riboflavin is a single link in a chain or in chains of reactions in which other vitamins are involved it would be surprising if the lesions produced by riboflavin deficiency were specific Machella and MacDonald (1943) who quote other similar observations report cases of cheilosis that were not improved by treatment with not less than 6 milligrams of riboflavin per day but were healed with brewer s yeast Smith and Martin (1940) reported cases of cheilosis and angular stomatitis that healed rapidly on treatment with pyridoxine. Spies *et al* (1945) consider that cheilosis seen in pellagrins, may improve on treatment with niacine only but that unless the diet becomes adequate the lesions tend to return even when the patients are taking niacine According to Reiss (1936) perlèche-like lesions may be seen associated with evidences of deficiency of vitamin A and may heal on treatment with cod liver oil In some investigations no relation has been found between the presence of any of the supposed signs of riboflavin deficiency and the amount of riboflavin in the diet. It can therefore be stated that these signs cannot be regarded as strictly pathognomonic of ariboflavinosis.

Other members of the B complex

Smith Smith and Callaway (1941) reported that dyssebacia—a condition in which plugs of dry sebaceous material which when removed and rubbed on a glass slide leave a greasy mark distend the follicles of the skin of the nose chin and forehead—may be cured by autoclaved yeast or liver extract, although vitamin B_1 riboflavin and niacine have no effect Joliffe and his colleagues (1942) obtained similar results. Gross (1941) also found that extensive eruptions, mostly seborrhoeic, were in some cases cured rapidly and in others considerably improved under treatment with injections of liver extracts.

Pyridoxine—One of the vitamins contained in yeast and liver extracts is pyridoxine. Rats deprived of this vitamin suffer from a red scaly dermatitis, with oedema, of the paws, the tips of the ears and the tail. The amount of pyridoxine required by human beings is not known. The order of the amounts in an ordinary diet is indicated by the daily amounts contributed from various foodstuffs milk (2 pints per week) 0·05 milligram meat (1 pound per week) 0 3 milligram flour (6 3 ounces per day) 0 53 milligram Dry food yeast contains 1 2–2·4 milligrams and dry brewer s yeast about 1·4 milligrams per ounce. The effect of doses, which are large compared with the amounts in an ordinary diet or in doses of yeast, on

expected that treatment with a vitamin will have any effect, unless the doses given exceed the normal intake. There are mixed vitamin preparations on the market in which the amount of some members of the B group, particularly riboflavin, are small compared with either minimal requirements or the average daily intake.

The vitamins of the B group occur together in foodstuffs deficiency of one member is usually associated with deficiency of others. Some co-operate in their action It has been reported that treatment of pellagra with niacine alone may even aggravate some of the signs of the disease. Not all of the vitamins of this group have been identified, and some of those identified cannot be obtained for general use. It is therefore reasonable to use preparations of liver yeast, or wheat germ which contain the known and possibly unknown members, for the treatment of deficiencies of the B group The liver extracts should be crude the purified extracts contain the anti-pernicious-anaemia factor with as little else as possible. Unfortunately we do not know what vitamins are retained in the various crude liver extracts.

It may be difficult to give enough of some of the vitamins when these preparations are used. Hughes (1946) found that 4 grammes of food yeast per day were not enough to cure severe lesions due to deficiency of riboflavin among prisoners in gaols in Lagos, but that 9 grammes were enough to cure these lesions in about 12 weeks. After injection of 10 milligrams of riboflavin severe lesions disappeared in 1 week. The dose of 9 grammes of yeast contains only 0·45 milligram of riboflavin. Some people are unable to tolerate larger doses of yeast (Accessory Food Factors Committee 1945c). Marmite contains 1 5 milligrams of riboflavin per ounce, so that ½ ounce is needed to supply the minimal effective dose. Food yeast contains about 0·01 milligram of biotin in 9 grammes

The doses of pyridoxine used, for example, by Wright (1942) are more than can be given as yeast In the treatment of agranulocytosis there is no time for making experiments it is advisable to continue to give the huge doses used by Cantor and Scott (1945) but, in the treatment of chronic diseases of the skin, the efficiency of smaller doses might be tried. Joliffe and his colleagues (1942), after finding a dose of 10 milligrams of pyridoxine per day effective in the treatment of acne, suggest the use of yeast but the possible doses of yeast will supply at most, only 0·7 milligram per day When we use the vitamins of the B group in treatment, we are faced with a dilemma either we may not give all the vitamins of this group which are needed or the doses may be too small It may be that this dilemma accounts, in part, for the variability of the results obtained in treatment of what appears to be the same disease, with individual vitamins or with preparations of vitamins. Probably the best line is to administer large doses of the vitamin of which a particular deficiency is suspected and to give simultaneously polyvalent preparations such as those of yeast.

AMINO ACIDS

Keratin contains a higher proportion of cystine than is found in most other proteins. As it contains sulphur the cystine of newly formed keratin must come from the sulphur-containing amino acids of the proteins of the food or of the body Excessive formation of skin keratin may require more cystine than is

Intestinal organisms can synthesize all known members of the B complex. The introduction of the insoluble sulphonamides, which are used to inhibit the growth of bacteria in the intestine, has afforded a new method of study of the extent to which animals can depend upon this synthesis for their supply of vitamins. By this means it has been shown that rats can utilize pantothenic acid, biotin and folic acid synthesized in their intestines.

The evidence that human beings may obtain a large proportion of their supply of niacine in the same way has been mentioned already The amount of *p*-aminobenzoic acid folic acid and pantothenic acid contained in the urine and faeces together may commonly exceed the intake (Denko *et al* 1946) the intake of biotin may be $\frac{1}{3}$–$\frac{1}{6}$ of the amount in the urine and faeces and less than the amount in the urine alone (Oppelt 1942 Gardner *et al.*, 1946) The experiments of Najjar and Holt (1943) suggest that some human beings may like refective rats, be able to absorb sufficient vitamin B_1 synthesized in their intestines, to keep them free from any evidence of deficiency for a long time.

> A group of healthy young men were kept on a diet that supplied, every day between 0 1 and 0 2 milligram of vitamin B_1, which is considerably less than the supposed minimal requirement. After some months vitamin B_1 was excluded entirely from the diet Four of these subjects showed no signs of deficiency during the next 7 weeks. The faeces of these 4 contained over 0·03 milligram of vitamin B_1 per day, while the faeces of the others contained less. The amount of vitamin B_1 in the faeces of 1 of the subjects who excreted over 0·03 milligram was reduced when doses of succinylsulphathiazole were given.

Najjar and Barrett (1945) consider that these experiments show that human beings can absorb biotin and folic acid sufficient to meet their requirements, from amounts synthesized by micro-organisms in their intestines Najjar and his colleagues (1943 and 1945) have also shown that when the intake of riboflavin by human beings is low (0·07–0·09 per day) the amount of riboflavin in the urine may exceed the intake and the amount in urine and faeces be 5–6 times the intake The amounts excreted were not affected by dosing with succinylsulphathiazole Najjar and Holt (1945) agreed with Ellinger and Coulson (1944) that the amount of products of the metabolism of niacine in the urine might be more than was accounted for by the niacine in the food, but they did not find that the amount in the urine was reduced by treatment with succinylsulphathiazole. So it appears that some of the micro-organisms that synthesize vitamins in human intestines may be sensitive to the sulphonamides while others are not and that the niacine may be synthesized both by sensitive and insensitive organisms

It is possible that human beings depend upon synthesis by bacteria in their intestines for part of their supply not only of niacine, but also of pyridoxine and, especially biotin and that administration of the insoluble sulphonamides, or of penicillin by the mouth may cause deficiency of these vitamins.

Dosage

If a vitamin is given in order to supplement a deficient diet, the amount given should be at least one-third of the accepted minimal requirements. For example, if the diet contains 1 milligram of riboflavin 0 5 milligram at the very least should be given. When no such deficiency in the diet is suspected, it can hardly be

DISCUSSION

We know far less about the essential functions of vitamins we have no knowledge of the part that vitamins play in the regulation of the structure of the skin Only in the case of vitamin A have we any evidence of the nature of the control of a vitamin on the development of epithelium and in no case do we know how the control is exercised. Stannus (1944) has proposed the theory that, in the absence of riboflavin (niacine, also, should be included), the normal respiration and metabolism of the endothelial cells of capillaries suffer and that this, in turn, leads to a disturbance of the surrounding medium and so to a metabolic disorder of the cells of the neighbouring tissue. He considers that when the skin is very thin or is specialized as at the orifices of the body it is particularly liable to injury in this way On this hypothesis it is difficult to account for the differences usually found between the skin lesions of niacine and of riboflavin deficiency It is possible that other enzyme systems, in which the B-group vitamins take part are involved in this control of development. This control, whatever its nature, may as in the case of vitamin A, be one of a set of factors that influence the development of the skin in one direction or another

In the case of vitamin A again we have an example of the regulation of the mobilization and transfer of a vitamin from the food supply (or from stores in the liver) to the tissues, such as the retina, in which it is used

The balance between the various factors that regulate the development or metabolism of cells may be upset, either at any stage of the supply of such a controlling nutrient from the intake of food to the transfer to the tissues, or by excessive action of other factors It is possible that a lesion caused by deficient supply or a fault in the metabolism of a nutrient may be indistinguishable from one caused by factors unconnected with nutrition.

As matters stand, the use of vitamins to treat skin diseases, other than those that can be regarded as specific evidences of some deficiency must remain empirical. We have no theoretical reason for supposing (for example) that pyridoxine is any more than one of the host of remedies which have been hailed as remedies for acne but it is essential that treatment with nutrients should be combined with full investigations by the methods which are now being developed. We can learn much about the effects of nutrients on other parts of the body from experiments on other animals but human skin differs so profoundly from that of other animals in its structure and functions and in the way in which it is treated, that we can learn about it only from studies on human beings.

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supplied in the food and may cause a drain on the other proteins of other tissues. We have a parallel in the greater effect of deficiency of glycine and arginine in rapidly feathering breeds of chicks, as compared with the slower-feathering breeds, owing to the greater demands for the feathers (Hegsted *et al.*, 1941) Peters (1945) found that the scales shed by a man suffering from exfoliative dermatitis contained only 3 per cent of cystine, calculated from the sulphur content. This patient had oedema and ascites and was apparently dying. He was treated with cystine 11 days after treatment had begun the oedema had disappeared, the general condition improved and his skin became normal.

The oedema in this case may have been due to a low concentration of proteins in the serum caused by the drain on the body proteins to supply cystine. It is significant that cystine has a special stimulating action on the formation of plasma proteins (Madden *et al* 1943) Reduction of the serum protein has been described in erythrodermia desquamativa and eczema (Glaser and Markson 1945). In these cases also the loss of cystine and of other amino acids may have led to the reduction of the serum proteins

DISCUSSION

Consideration of the metabolism and functions of amino acids helps us to appreciate the problems that arise in the study of the relation of vitamins to disease. In the case reported by Peters (1945) the limiting factor in the formation of keratin and serum proteins was cystine but other amino acids are involved in the processes concerned—the formation of keratin of serum proteins the example of the effects on rapidly feathering chicks shows that cystine may not be the only limiting factor in the process These amino acids are interdependent keratin cannot be formed if one amino acid is missing, however plentiful the others may be. In the case of the vitamins of the B group we know that two at least—riboflavin and niacine—are both involved in one chain of enzyme reactions. In other processes, including the control of the structure of the skin we do not know how far vitamins are interdependent. Although certain defects may be regarded as specific evidences of deficiency of certain vitamins, we do not know that these are due to deficiency of or to a fault of metabolism of one particular vitamin.

We know that cystine must be supplied as such or formed from methionine we know how much is supplied by food and that if more is needed the demand must be met by a drain on other tissues but it now appears that we may get an extra supply of the B group of vitamins from the synthesis by micro-organisms in our intestines, and that we may even get more niacine and biotin from this source than from our food The actual supply of these vitamins, therefore, is uncertain and can only be estimated roughly by some indirect method such as that used by Ellinger and his colleagues (1944 1945)

We know that amino acids are used for building proteins, and this may be the only purpose for which cystine was needed in the case quoted but the work of Croft and Peters (1945) on nitrogen metabolism after burns shows that at least one amino acid—methionine—is used for some other purpose for if the methionine supplied is used for incorporation in the proteins of new tissue, others of the indispensable amino acids would be needed with it methionine alone would not reduce the loss of nitrogen.

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CHAPTER 5

THE BIOCHEMISTRY OF SKIN

R. A. PETERS and R. H S THOMPSON

COMPARED with that of many other tissues, the biochemistry of skin has, until recently received little attention And yet, in view of its exposure to heat and cold, to excessive variations in humidity resulting from prolonged sweating or from dehydration from external causes, to de-fatting from contact with organic solvents, as well as exposure to noxious chemical substances or pathogenic bacteria, it is perhaps of all the tissues of the body the one whose metabolism is most likely to become deranged Moreover any disorder in its metabolism may clearly exert effects of general importance an example of this is the dehydration and other dis turbances of blood chemistry that may accompany extensive thermal burns of the skin

Owing to the use of an ever widening range of potentially irritant chemicals in industry as well as the recent revival of interest in skin pathology in relation to chemical warfare vesicants, it is an opportune moment to review the present posi tion of our knowledge of the biochemistry of skin It is not intended to discuss in this chapter the known facts regarding the chemical constituents of skin Essential though these are such facts serve more as the substratum on which the biochemist works and are not immediately relevant *en bloc* to an understanding of the dynamic biochemistry of the skin or of how derangement of skin meta bolism can lead to alterations of its function Instead an account will be given of the enzymes and biochemical reactions of skin cells by means of which energy is obtained for their various processes, or by which their special functions, such as the synthesis of keratin or melanin are carried out

It must be realized at the outset that from the biochemist s point of view so far from being an inert tissue as skin has in the past been regarded by some, the integument represents a very complete and active system—complete because, like red bone marrow or testis, it contains, in addition to the enzymes reponsible for the degradative energy yielding reactions, the mechanisms responsible for constant new protein formation and cell divisions

RESPIRATORY METABOLISM OF SKIN

Since all the active functions of skin depend upon the provision of an adequate supply of energy it is natural to begin this survey with an account of the energy yielding reactions of the respiratory metabolism

Cellular respiration is studied by means of the micromanometric technique introduced by Barcroft and Warburg, the tissue being sliced or minced in order to allow access of oxygen and substrates to the respiratory cells In the case of skin

slices have usually been employed, although in young small animals, rats or mice, for example, the skin is sufficiently thin to allow adequate penetration of oxygen into the cells of an unsliced sample scraped free from underlying fat and connective tissue.

The respiratory activity of whole skin is low its rate of oxygen consumption being only ⅓ to $\frac{1}{15}$ that of brain, muscle or liver (Wohlgemuth and Klopstock, 1926 Bohmann, 1936 Amersbach, Nutini, and Cook, 1941). However when allowance is made for the relatively large amount of metabolically inert material (keratin and collagenous fibrous tissue) contained in skin it will be seen that the respiratory activity of the cellular parts cannot be far below that of other tissues which indeed is only to be expected when the activities of the basal cell layer and of the sebaceous and sweat secreting cells are taken into account.

This is revealed by the effects that the age of the animal has on the respiratory activity of its skin, these effects being due probably to variations in the amount of collagenous fibrous tissue present. Loebel (1925) for example found an unusually high rate of oxygen uptake of the skin of newly born white mice Needham and Dixon (1941) have recently confirmed this in the case of young rat skin, while Adams (1937), also using rat skin, has demonstrated a steady fall in respiratory rate during the first 200 days of life

Little work has so far been done in an attempt to analyse these respiratory processes, in the sense of determining the relative rates of oxidation of different possible substrates. Such an analysis is rendered difficult on account of the relatively small size of the increase in respiration brought about by the addition of oxidizable substrates to skin *in vitro* Thompson (1946a) studied the oxidation of sodium pyruvate, CH_3-CO-COONa, and sodium succinate COONa-CH_2-CH_2-COONa, by rat skin slices. Pyruvic acid is an essential intermediary in the cellular catabolism of carbohydrates, while succinic acid has recently been suggested as playing an essential catalytic role in carbohydrate oxidation (Krebs, 1943) With skin, pyruvate was found to produce a small increase in respiration, succinate rather more. Needham and Dixon (1941) have also stated that glucose exerts little effect on oxygen uptake The meagre effects produced by addition of these substrates to skin, in contrast to their large effects on the respiration of say nervous tissue may be due to the store of carbohydrate which is normally present in skin (Seller and Spera, 1938) and which may be sufficient to maintain the respiration at an almost maximal rate in the absence of added carbohydrate. Further evidence however of the ability of skin to metabolize pyruvic acid was produced by Peters and Wakelin, who in 1943 demonstrated the presence of vitamin B pyrophosphate ("co-carboxylase") in rat skin earlier work, largely with brain tissue, had shown that this ester of vitamin B is an essential co-enzyme for the oxidation of pyruvic acid in animal tissues (Peters, 1936a). More recently still the total content of vitamin B (aneurine or thiamine) in rat skin has been assayed (Paul Paul, Taylor and Marsters, 1945), a value of 0 57 $\mu g./g.$ of skin being obtained it is of interest to note that this amount is approximately doubled in the repair tissue filling skin wounds.

Despite the accessibility of various toxic agents to epidermal cells, and the increase in recent years in the incidence of occupational dermatoses, little information

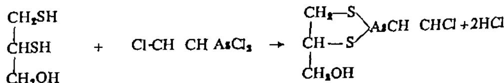
is again available on the action of toxic substances on the respiratory metabolism of skin. Of the few compounds studied both cyanide and iodoacetate have been shown to inhibit the oxygen uptake of frog's skin (Huf 1936, 1938 Francis and Gatty 1938) in this connexion it may be pointed out that iodoacetate produces vesication of skin a fact which was commented on by Peters (1936b) when he demonstrated that both iodoacetate and the sulphone of mustard gas are inhibitors of the pyruvate oxidase system of brain

Phenylmercuric nitrate, even in dilutions of 1 100 000 also decreases the respiration of rats skin (Cook, Kreke, Eilert, and Sawyer 1942) This action, it was claimed, could be prevented by the presence *in vitro* of yeast extracts, without ffecting the germicidal properties of the mercurial.

During the recent war however important progress was made in this field in the course of work on the mechanism of vesication produced by the blister gases. Following up the indications provided by earlier work (Peters, 1936b, c) the problem of vesication was attacked by investigating the possibility of enzyme inactivation in the skin, and substantial evidence was produced supporting the enzyme theory of vesication This theory assumes that inhibition by the vesicant of an enzyme in skin essential for its normal metabolism and the maintenance of the normal permeability of the skin cells is the first step in the sequence of pathological derangements that leads ultimately to the blister

In the case of the arsenical blister gases it was found that the enzyme system responsible for pyruvate oxidation undergoes extensive inhibition in the contaminated skin (Thompson 1946a) This action of arsenic compounds was studied in the first instance by examining the effects produced by the addition of small concentrations of sodium arsenite to slices of normal skin respiring *in vitro* and later by comparing the rates of pyruvate oxidation in normal skin and in skin that had been contaminated *in vivo* with lewisite (β-chlorovinyldichlorarsine, $Cl{\cdot}CH\ CH\ AsCl_2$) The oxidation of succinate by the contaminated skin on the other hand, proceeded normally Arsenic compounds seem therefore, to exert a specific effect on the respiratory metabolism of skin, as they do on the oxidative systems of the tissues generally (Peters, Sinclair and Thompson 1946)

From the point of view of therapy a real advance was made, as a compound was discovered (Stocken and Thompson 1941 1946a) which was capable of protecting the pyruvate oxidase system of brain from inhibition by arsenicals, and also of reversing this inhibition when once established (the brain enzyme was used in the the initial tests for reasons of technical convenience) This compound is 2, 3-dimercaptopropanol [1] (British Anti lewisite or BAL') It has been shown that it reacts with arsenicals to form a relatively stable cyclic derivative



[1] The Council on Pharmacy and Chemistry of the American Medical Association has recently (1946, *Journal of American Medical Association* 131 824) recommended the adoption of the non-proprietary name of Dimercaprol.

The addition of this compound prevents the inhibition of pyruvate oxidation by lewisite in skin slices, and when applied to skin even one hour after contamination with lewisite it causes a substantial increase in the rate of removal of arsenic from the contaminated area this removal of arsenic from the skin is accompanied by increased excretion of arsenic in the urine (Stocken and Thompson, 1946b). In man visible evidence of the reversal of the changes in the skin leading up to the formation of the lewisite blister is obtained, since if British Anti-lewisite is applied to the skin as late as one hour after contamination with undiluted lewisite, the erythema and oedema already present subside in the course of the next few hours, instead of progressing, as in an untreated site, to the development of a well-filled vesicle on an ultimately necrotic area of skin. This work with experimental lewisite contamination and with accidental arsenical burns in factories has now been extended to cases of post-arsphenamine dermatitis both in this country and in the United States of America. Although the picture here is complicated by sepsis of the denuded skin and by the difficult factor of hypersensitivity the results have on the whole been definitely favourable, and in some instances dramatic (see Peters, Stocken, and Thompson, 1945 Carleton, Peters, Stocken Thompson, and Williams, with Appendix by Storey Levvy and Chance, 1946). In enzyme experiments British Anti-lewisite is able to detoxicate therapeutic compounds of gold (Thompson and Whittaker 1946) It is possible, therefore, that it may be of value in the treatment of gold dermatitis as well.

Turning to the general problem of vesication Peters and Wakelin (1940) have shown that the pyruvate oxidase enzyme system is also inhibited, though less acutely by mustard gas and related compounds. A further line of *important* evidence in favour of the enzyme theory has been developed in Cambridge. Needham and Dixon (1941) have studied the action of a *wide range of vesicant* substances on carbohydrate catabolism, and have shown that such substances are active inhibitors of the glycolytic mechanism in skin responsible for the breakdown of carbohydrates. But while the *anaerobic formation of lactic* acid from glucose was found to be strongly inhibited by these vesicants, lactic acid formation from hexosediphosphate proceeded normally It seemed likely therefore, that some component of the system responsible for the *initial phosphorylation* of glucose in skin, such as hexokinase, might be the factor attacked, and further work showed this to be the case.

Hexokinase is of fundamental importance in the breakdown of sugars, in that it catalyses the transfer of phosphate groups from

Glucose Adenosine triphosphate

→Glucose-6-phosphate + Adenosine diphosphate

adenosine triphosphate (ATP) to glucose, the phosphate ester of which then undergoes degradation with evolution of energy This enzyme had not previously been demonstrated in skin, nor indeed had cell-free glycolysing extracts been obtained from skin. The presence of hexokinase implies that glycolysis in skin is of the phosphorylating type as in muscle. Among the vesicants studied were a number of arsenical compounds and methyl bromide, all of which were found to inhibit hexokinase (Dixon and Needham, 1946).

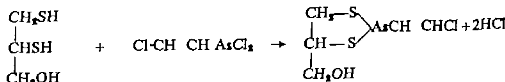
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work on thermal burns, stimulated by the recent war has provided definite proof of the existence of skin proteinases. In the skins of man and of the rabbit, guinea-pig and rat, a proteolytic enzyme has been demonstrated (Beloff and Peters, 1945), which is partly extractable from the skin. It is active at neutral and alkaline pH and shows optimal activity at pH 7 5. It is not, however identical with trypsin. This point was established by examining its action on the synthetic peptide, benzoyl-l-arginineamide Bergmann and Fruton (1939) have shown that this peptide is attacked by trypsin more readily than any other synthetic peptide, and have concluded that the particular -CONH linkage contained in this compound is specifically adapted to hydrolysis by this enzyme It was found that neither this peptide nor Bergmann s specific peptide substrate for chymotrypsin (carbobenzoxy l-tyrosyl-glycine amide) was split by the enzyme in skin. Beloff and Peters (1945) also established the presence of a second proteolytic enzyme in extracts of rat skin this was shown to be a peptidase capable of splitting the synthetic tripeptide d,l-leucyl-glycyl-glycine. Zamecnik, Stephenson, and Cope (1945) confirmed the presence of this enzyme in extracts of dog s skin, as well as in the bleb fluid collected from human burns, and have designated it tentatively as an aminoexopeptidase

The relation of skin proteinases to the phenomena of desquamation and vesication has been raised by the recent observations of Medawar (1941) which suggest that the release of proteinases in an abnormal position in the skin may prove dangerous, since he has shown that digestion with trypsin will separate the epidermis from dermis in sections of human skin made by the dermatome The skin proteinase of Beloff and Peters is not more than 25 per cent inactivated by an exposure to 70° C for 5 minutes, a temperature which has been shown to produce considerable damage to skin in less than one minute. It may therefore be liberated by heat in an active form from its normal, physiological location in the skin. At the same time it has been shown that in the rat there is a decrease in the proteinase content of skin after exposure to heat owing to the passage of the enzyme into the circulation, and they have advanced the view that it is this leakage of proteinase from the skin cells which initiates the loosening of the epidermis prior to blister formation. In this connexion it is interesting to note that Cullumbine and Rydon (1946) have found that Menkin s leucotaxine is liberated from proteins by treatment with the skin proteinase.

In addition to this leakage of proteinase the aminoexopeptidase splitting d,l-leucyl-glycyl-glycine has also been found to increase sharply in the lymph draining a burned area of a dog s extremity (Zamecnik, Stephenson, and Cope, 1945). Consistent with this, Perlmann, Glenn, and Kaufmann (1943) had earlier detected by electrophoretic analysis the existence of a new protein entering the lymph from a burned area. Although the degree of local protection in the skin is probably slight, the entry of these proteolytic enzymes into the circulation is not as dangerous as might be expected, because of the presence in blood of a specific anti-proteinase associated with the most soluble albumin fraction of the plasma (Beloff 1946).

It will be seen therefore, that two essential cellular components, the pyruvate oxidase system and hexokinase, both concerned in the energy yielding reactions of carbohydrate breakdown are thrown out of action by contamination of skin with lewisite, mustard gas and a number of other chemical vesicants. Disorganization of these systems could without doubt, according to the adherents of the enzyme theory initiate changes of sufficient severity to the epidermal and capillary endothelial cells to upset their normal permeability relationships and so allow the development of local changes leading up to blister formation

The respiration of skin during wound healing has been studied by von Gaza and Gissel (1932) They claimed that, following the production of experimental superficial skin incisions, the wounded area of skin shows a significant reduction of oxygen uptake at the end of 12 hours by 24 hours the respiratory rate had returned to normal and by 2½ days was showing a marked increase above the original level this increase corresponding presumably to the period of active tissue regeneration The level of anaerobic glycolysis (lactic acid production in the absence of oxygen) showed a similar sequence of changes

In 1940 Berenblum, Chain, and Heatley carried out an interesting comparison of the oxygen consumption aerobic and anaerobic glycolysis, and respiratory quotient of normal rabbit skin epithelium (separated as far as possible from corium) and Shope papilloma. They found that their values for the papilloma were identical with those obtained with the normal tissue. The authors concluded that their finding that normal skin epithelium shows aerobic glycolysis and a low respiratory quotient (0 7 for normal epithelium 0·6 for papilloma) is further proof that these properties cannot be regarded as characteristic of a neoplastic disturbance.

In the course of a study of the effects of thermal burns on skin metabolism begun in 1941 by Manifold and Peters, Rossiter (1942) found that whole young rat skin as opposed to rabbit skin epithelium, had a respiratory quotient of 0 87 No significant effect on skin respiration was produced by heating young rat skin for 10 minutes at 43° C. Heating at 48° C., however caused a marked fall in oxygen uptake and a lesser fall in anaerobic glycolysis aerobic glycolysis on the other hand was increased while the R.Q remained unchanged. Application of a burning iron (Leach Peters, and Rossiter 1943) at 45° C. for one minute to the skin of a live guinea-pig causes no change in oxygen uptake after a burn at 50° C. there is a slight fall and at 55° C. a marked fall in respiratory rate.

PROTEOLYTIC ENZYMES OF SKIN

By analogy with other tissues it can be inferred that skin must depend upon the presence of proteolytic enzymes for the synthesis and degradation of its proteins. Indeed, in view of the special synthesis of keratin by the epidermal cells and the formation of collagen and elastin in the corium, in addition to the normal protein metabolism common to cells of all tissues, the proteinases of skin should be of particular interest.

From time to time there have been observations suggesting the presence of proteolytic enzymes in skin but these have not been convincing. More recently

salts, so that the possibility still exists that this may be the parent substance even though tyrosinase has been proved to be present in normal skin. Tyrosinase and the polyphenol oxidases of plants (potatoes and mushrooms) have been shown to be copper proteins (Kubowitz, 1937 Keilin and Mann, 1938 Dalton and Nelson, 1939), a fact of interest in connexion with the essential role that copper is known to play in animal nutrition.

The relation of the activity of the adrenal glands to melanin formation is still the subject of much work. Contrary to some earlier reports which tended to throw doubt on the postulated connexion of the adrenals with skin pigmentation in animals, Ralli and Graef (1943) have recently claimed that adrenalectomy in rats causes a marked stimulation of the hair follicles with an increased deposition of melanin and an accompanying increase in dopa-oxidase activity

Other steroid hormones (certain of the oestrogens and androsterone) have been shown to produce increased pigmentation when implanted subcutaneously in pellet form into rats (Forbes, 1942). It appears that the action of these substances is a purely local one influencing melanoblast function.

Much uncertainty still exists concerning the details of the connexion of certain of the water-soluble vitamins of the B group with hair and skin pigmentation. Deficiencies of pantothenic acid (Unna, Richards, and Sampson 1941 Sullivan and Nicholls, 1942 Gross, Harvalik, and Runne, 1941 Dann, Moore, and Frost, 1942) p-aminobenzoic acid (Martin and Ansbacher 1941) biotin (Emerson and Keresztesy 1942 Sullivan and Nicholls, 1942) and folic acid (Martin 1942) have each been claimed to lead to greying of the hair (achromotrichia) in rats But until these results have been confirmed and extended, final judgement on the relation of these factors to melanin formation must be suspended. Whether this is the common reaction of the pigment-producing mechanism of the skin to a number of different metabolic disorders, or whether deficiency of these several water-soluble factors leads to a common metabolic derangement which in turn is responsible for the defect in pigmentation is not yet clear

Administration of thiouracil has also been observed to produce changes of pigmentation in capons and cockerels, the usual black pigment of the feathers being replaced by red (John, 1944 Domm and Blivaiss, 1944) this is of interest in view of the demonstration by Paschkis, Cantarow Hart, and Rakoff (1944) that melanin formation by the tyrosine-tyrosinase system is inhibited by thiouracil since thiouracil can combine with copper and since this inhibition can be largely prevented by the addition of copper it provides presumptive evidence that the enzyme in skin responsible for melanin synthesis contains a copper-protein component, like the plant phenol oxidases.

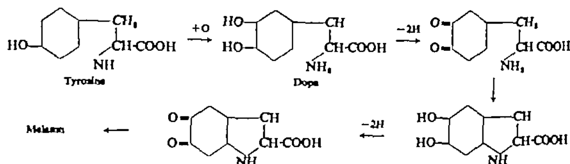
SPREADING FACTORS AND HYALURONIDASE

In connexion with problems of bacterial invasiveness and capillary permeability the demonstration by Meyer Chaffee, Hobby and Dawson (1941) of the presence of hyaluronidase activity in skin is of great interest.

The occurrence of a spreading factor (Duran-Reynals, 1928 McClean, 1930) in rabbit skin was first reported by Claude and Duran-Reynals in 1934 These

PHENOLASES AND MELANIN PRODUCTION

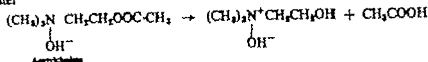
One aspect of the biochemistry of skin in which advances were early made is the problem of melanin synthesis It is now believed that melanin is formed ultimately from a phenolic precursor and considerable light has been thrown on the changes involved The existence of a phenolase in mammalian skin has been known since the demonstration by Bloch (1917) of the presence of an enzyme which he called dopa oxidase in epidermis. Using a histochemical technique he showed that this enzyme in skin brought about the formation of melanin from dopa (dioxyphenylalanine, or more correctly dihydroxyphenylalanine) The probable chemical changes involved in this synthesis were worked out by Raper and his colleagues (see Raper 1932) in the course of their study of the enzyme tyrosinase. This enzyme, occurring principally in plant tissues, converts the amino acid tyrosine into a red pigment which in the presence of oxygen is then changed into a black melanin like substance without further enzymatic participation The stages involved are shown below



It will be seen that dopa is the first intermediate to be formed in this series of changes It will be noticed however that whereas tyrosine is a monophenol dopa is a diphenol and although tyrosine can act as the starting-point for the synthesis of melanin when catalysed by a non-mammalian tyrosinase, the existence of a monophenol enzyme has never been convincingly demonstrated in normal skin dopa-oxidase being by definition a polyphenol oxidase. It is true that in 1917 Onslow prepared extracts of the skin of black rabbits which were able to oxidize tyrosine and *p*-cresol another monophenol But Pugh (1933) while demonstrating clearly the existence of a polyphenol oxidase, only obtained monophenolase (tyrosinase) activity in some cases. Yamasaki (1924) had previously been unable to detect any monophenol enzyme in human skin although dopa was readily oxidized. Turning from normal skin to tumour tissue, however Hogeboom and Adams in 1942 showed conclusively the presence of tyrosinase in extracts of a mouse melanoma both tyrosine and dihydroxyphenylalanine were rapidly oxidized phenylalanine being unaffected.

While the enzymatic nature of melanin formation can therefore, be regarded as finally established the parent substance from which it is formed in normal skin is still uncertain. Rothman (1942) however has shown that although the presence of dopa has never been demonstrated in skin, tyrosine can be converted *in vitro* into dopa by ultra violet irradiation in the presence of ferrous

More recently Thompson and Whittaker (1944) have described experiments on the esterases of skin, primarily from the point of view of a study of the ability of skin to split acetylcholine. Both rat and human skin were shown to contain a specific cholinesterase. This enzyme splits acetylcholine into acetic acid and choline, the latter being very much less active pharmacologically than its acetyl ester



$$\underset{\text{Acetylcholine}}{(CH_3)_3\overset{}{N}(OH^-)\,CH_2CH_2OOC{\cdot}CH_3} \rightarrow (CH_3)_3N^+(OH^-)CH_2CH_2OH + CH_3COOH$$

The cholinesterase in skin was found to be highly sensitive to inhibition by eserine, and to be distinct from a non-specific esterase also present, capable of splitting simple esters and fats such as methyl butyrate and tributyrin.

From the earlier physiological work of Langley Dale, Lewis, and others on the innervation and vascular reactions of the skin it was probable that certain of the structures in skin would be associated with cholinesterase activity It has been suggested too that certain pathological conditions of the skin may be due to abnormal functioning of cholinergic nerves. Grant, Bruce Pearson, and Comeau (1936), for example, have concluded that certain cases of urticaria of nervous origin may be brought about by the release of acetylcholine in the skin as a result of stimulation of cholinergic nerve fibres. On the basis of ionization experiments, Lewis (1944) described the interesting finding that the skin of young women appears to be more susceptible to the action of choline esters than does that of young men. Whether this is related to possible differences in the levels of cholinesterase activity in the two skins is not yet known.

Turning to inhibitors of cholinesterase activity Alexander Elliott, and Kirchner (1940) have stated that eserine, introduced electrophoretically into the skin, is a powerful urticariogenic agent, even in dilutions of 1 10,000 and occasionally 1 100,000 Thompson (1946b) has shown that the cholinesterase of skin is inhibited *in vitro* by sodium arsenite, and *in vivo* by certain non-arsenical vesicants of the mustard gas type.

Of the phosphatases, an important class of enzymes hydrolyzing esters of phosphoric acid, Fell and Danielli (1943) have demonstrated the presence of an alkaline phosphomonoesterase in normal rat skin, and have shown that during the healing of a skin wound or burn the level of this enzyme in the regenerating tissue is considerably raised above the normal value.

NUTRITION OF THE SKIN

The pathological lesions of the skin in deficiency states are too well known to need description here Full accounts of them have been given in cases of deficiency of vitamin A riboflavin, nicotinic acid, and ascorbic acid, and the question of pathological involvement of the skin in pyridoxine (vitamin B_6) and pantothenic acid deficiencies has been raised. Except for the work designed to analyse the nutritional achromotrichias, the nature of the biochemical lesion in the skin in various avitaminous states has received little attention, though, by analogy with

substances have also been demonstrated in certain snake venoms, bee sting, Clostridium welchii toxin pneumococcus cultures and other bacterial species as well as in testis extracts and have been called spreading factors because of the increase in the permeability of the dermis and connective tissues which their presence brings about, thereby facilitating the rapid spread and degree of invasiveness of certain virulent bacteria In 1940 Chain and Duthie showed that various fairly pure spreading factors also exhibited hyaluronidase activity that is to say that the preparations were capable of hydrolysing hyaluronic acid a mucopolysaccharide built up of glucuronic acid and N acetylglucosamine units. The highly viscous hyaluronic acid appears to be depolymerized by the enzyme and then to be split into its glucuronic acid and N-acetylglucosamine components. Since the intact substrate hyaluronic acid is of a mucinous nature, the enzyme is sometimes referred to as a mucinase. Since neither hyaluronidase nor any of the spreading factors has yet been obtained in the pure state it would perhaps be premature to state that their identity has been proved but much evidence can now be brought foward in favour of the view that spreading activity is due to the enzymatic splitting of this mucopolysaccharide. It should be added for example, that Meyer and Chaffee (1941) have been able to demonstrate the presence of hyaluronic acid in a mucopolysaccharide mixture obtained from pig s skin.

Although the relation of hyaluronidase to problems of bacterial invasiveness has been considered in some detail in the literature on the subject, and is likely to be of great importance, little attention seems to have been given so far to its purely physiological role in skin and connective tissue, yet the results of activation or inhibition of this skin enzyme may well have an important bearing on the pathogenesis of certain non infective skin disorders.

SKIN ESTERASES AND FAT METABOLISM

Just as in the case of the skin proteinases, where keratin synthesis introduces a special biochemical function over and above the level of protein metabolism common to all cells, so in the sphere of fat metabolism the presence of the sebaceous glands introduces special problems of fat synthesis and secretion From the biochemical standpoint, however little is known about this function of the skin, although the existence of an active lipase in human skin was first shown by Yamasaki in 1924

It is well known from the work of Burr and Burr (1929) that certain essential unsaturated fatty acids are required for the maintenance of the normal condition of the skin. Although oleic acid with one double bond, is readily synthesized by warm blooded animals, they are unable to manufacture the more highly unsaturated arachidonic acid, $C_{20}H_{32}O_2$, with four double bonds, and clupanodonic acid $C_{22}H_{34}O_2$, with five double bonds unless unsaturated acids such as linoleic or linolenic acids are provided in the diet. Most of the experimental work in this condition has taken place with rats, and in these animals the absence of these unsaturated acids from the diet leads to a characteristic scaly condition of the skin. Williamson (1941) has described the thickening of the epidermis and other histological changes present in these fat-starved animals.

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other tissues, riboflavin and nicotinic acid are presumably acting as components of certain of the enzymes involved in the intracellular oxidative processes, the flavoproteins and dehydrogenases respectively

In view of the activity of the basal cell layer of the epidermis, involving cell reproduction the nutritional requirements of the skin might be expected to be great Visible involvement of the skin in a wide variety of different nutritional states is therefore not to be wondered at. Moreover the clinical conditions developing may not show a high degree of differentiation between the various deficiencies Follicular keratosis is an example of this, although fundamental knowledge of the changes underlying its development in deficiency diseases in man is not sufficiently advanced to warrant dogmatic statements. In two recent human trials carried out by the Medical Research Council however depletion of vitamin A over a period of approximately two years resulted in follicular keratosis in only one subject and in this case it was only doubtfully related to the deficiency whereas depletion of vitamin C produced definite skin changes, including follicular keratosis, in the majority of cases Indeed, Stannus (1945) has already pointed out that these changes may often represent the common reaction of a predisposed skin to a variety of disturbances in its normal metabolism, and cannot, therefore, in our present state of knowledge be regarded as diagnostic of any one deficiency state

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recent years have now put at his disposal. In this task the dermatologist has a precious advantage, for his trained eye can observe the influence of this or that product of the laboratory upon the separate structures that compose the skin, and, without difficulty supplement his observations microscopically To do this intelligently however considerable knowledge of both the clinical and scientific aspects of endocrinology is essential, and it is to be hoped that in the future there will be the same *rapprochement* between the dermatologist and the endocrinologist that Hoskins (1941) has sought to establish between the latter and the psychologist.

Hormonal activity at various ages

One of the most intriguing exercises in the art of observation and deduction that is available to the dermatologist is to study the various changes occurring in the skin at different ages, from early infancy to old age, and to attempt to correlate them with the waxing and waning of functional activity in the endocrine glands. The problem of the nature and origin of vernix caseosa the reaction in the skin, hair follicles, sebaceous and sweat glands to the stimulus of puberty ably reviewed by Desaux (1938) the disturbances of adolescence—that critical period of life when, as May (1938) remarks there should normally be a reversal of vago-sympathetic equilibrium, the relative vagotonia of childhood being succeeded, owing to increased activity of the thyroid and adrenals, by the sympatheticotonia that the future stress of adult life demands the influence of a normal sexual life or the lack of it, of pregnancy and of the psychological conflicts that may so profoundly affect the endocrine-autonomic system the female climacteric and its less defined and more tardy counterpart in the male finally the degenerative processes of old age—all these provide material for research for the dermatologist and the endocrinologist alike.

The problem of bisexuality

There is, too the problem of bisexuality which, since the so-called emancipation of women, is likely to provoke increasing speculation in the future. That all of us in varying degree are bisexual has long been realized, but the question to be answered is this what proportions between the characteristics of the two sexes produce the ideal man and the ideal woman? The answer probably differs according to whether one regards them as animals or as human beings, or whether they are to live under primitive conditions or to play their parts in modern social life. Obviously if the propagation of the species were all-important, the most virile man and the most feminine woman would be the ideals, but both have their disadvantages in the artificial atmosphere of civilization.

The former is ill-adapted to a sedentary life and an uneventful routine. He needs an occupation that imposes vigorous physical exertion, or at least scope for creative and constructive activities. Moreover he can hardly be expected to remain monogamous. His natural inclination is to live dangerously and he is apt to eat and drink to excess. To the dermatologist this latter tendency is of importance because (as I have insisted elsewhere (Barber 1929) and as is discussed below), given the necessary degree of androgenic stimulation of the skin, an intake of food (and particularly of carbohydrates, fats, and alcoholic liquor) disproportionate to the amount of physical energy expended is almost certain to result in the infective complications of the seborrhoeic state. Sabouraud (1932) admirably

CHAPTER 6

THE INFLUENCE OF THE SEX HORMONES ON THE SKIN AND PILO SEBACEOUS SYSTEM WITH A DISCUSSION OF THE AETIOLOGY OF 'SEBORRHOEIC ERUPTIONS

H W BARBER

GENERAL CONSIDERATIONS

THIS chapter is concerned mainly with the influence of the sex hormones derived from the gonads and the adrenal cortex upon the skin the hair follicles, and the sebaceous glands. It is thought to be preferable to review this important, though restricted, aspect of the relationship that exists between the endocrine system and the skin with its appendages, in the light of recent clinical and experimental observations, rather than to attempt a survey of this relationship in its entirety

Thanks to the biochemists, whose researches have provided us with the natural products of the endocrine glands in a chemically pure state, and in some instances with synthetically prepared substances possessing comparable physiological actions, the dermatologist now has the opportunity of testing, by accurate experimental methods, deductions arrived at by clinical observations. Clearly too in this field of research the histopathologist must see a fascinating prospect before him, for he may confirm under the microscope the macroscopical changes noted by the clinician

For example it is possible, by oestrogenizing a virile male, to change his complexion to a startling degree, and conversely that of a eunuch or female by injections or subcutaneous implantation of testosterone Such experiments are considered below but it is obvious that they concern not only the clinician and the histopathologist, but also the bacteriologist, since it would appear that the sex hormones influence in opposite fashion the growth of the natural flora of the skin.

An introduction to this subject demands a tribute to a great man—R. Sabouraud Primarily a bacteriologist and mycologist, he became a very astute clinician He, more than any of his predecessors or contemporaries, was aware of the influence on the skin and the pilo-sebaceous system of the gonadal functions and of the different phases of sexual evolution and involution in human beings His original studies of the bacteriology and mycology of the skin, like those of Unna on its histopathology will remain classics for all time, and it is impossible to over-estimate the influence of these two pioneers That their conclusions were sometimes erroneous is of no moment. To them above all belongs the credit of bringing to the aid of clinical observations the more exact methods of laboratory research in dermatology

In their day the scientific study of the endocrine glands and of the closely linked autonomic nervous system was in its infancy Once again, however laboratory workers have earned the gratitude of the clinicians and their patients and it is for the clinician to make full use of the material that the intensive researches of

recent years have now put at his disposal. In this task the dermatologist has a precious advantage, for his trained eye can observe the influence of this or that product of the laboratory upon the separate structures that compose the skin, and, without difficulty supplement his observations microscopically To do this intelligently however considerable knowledge of both the clinical and scientific aspects of endocrinology is essential, and it is to be hoped that in the future there will be the same *rapprochement* between the dermatologist and the endocrinologist that Hoskins (1941) has sought to establish between the latter and the psychologist.

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illustrates this point in his description of les hommes trop nourris *Le sujet est visiblement trop nourri haut en couleur son visage est couperosique et présente souvent par places de l acné pustuleuse miliaire de surface Combien de misères cutanées surviennent alors qu une vie physique mieux réglée aurait empêchées de naître Que cet individu cesse de boire et de manger avec excès qu il fasse à l exercice physique sa part légitime qu il maigrisse de 500 à 800 grammes par mois pendant six mois et tous les phénomènes pathologiques qu il présente s amenderont peu à peu* He then proceeds to describe such conditions as pustular folliculitis and furunculosis, acne necrotica, and seborrhoeic dermatitis

The ultra feminine woman, in contrast is not fitted either by temperament or by physique to endure the stress of competitive activities in business or professional life, or to indulge in severe physical exertion. She is by nature placid and submissive, and her instincts are maternal, her interests centred in the home. She is not irked by routine tasks, nor has she the urge towards creative and original work. Affectionate and devoted as she may be to her husband, her feelings are essentially maternal rather than sexual and, though she may be unfaithful this is due to a natural feminine desire to please the male rather than to the sexual urge that dominates the vamp and is a masculine characteristic. This is well illustrated by Somerset Maugham s remarkable study of the physical and psychical attributes of Rosie in his novel *Cakes and Ale*

The masculine and the feminine libido are, in fact different in nature, the former possessing an aggressive quality the latter being submissive. It has been found that testosterone is more effective than are oestrogens in the treatment of frigidity in women.

The morphological and psychological characters of the two sexes have been admirably contrasted by Cawadias (1946) he points out that for every individual *a balance sheet of sexual characters can be composed* For this purpose a knowledge of the influence of androgens and oestrogens respectively on the skin and pilo-sebaceous system is essential From both clinical and experimental observations this knowledge is now fairly accurate and it has revealed how very commonly a considerable degree of masculinity is present in the female of to-day not only during adolescence and after the climacteric. Judging from the paintings and portraits of girls and women of generations past, it seems to be likely that the *growing participation of females* in the stress of masculine occupations and sports has led to increased activity of the adrenal cortex with a relatively excessive production of androgen It is recognized that during the recent war menstrual irregularities developed in a considerable proportion of girls and women in the Services, and I have been struck by the frequency with which seborrhoeic dermatitis, acne, and even mild hirsuties appeared in them for the first time. Cawadias, indeed asks Is it not possible that, while retaining maternal organs, the female continues to evolve towards masculinity as regards other features? This may be true, but personally I doubt whether it is entirely a question of evolution, and would stress rather the influence of the change in the feminine mode of life.

The whole problem of bisexuality in its widest sense is, however extremely complex, for one has to consider the genetic factor the masculinizing influence of the foetal adrenal gland upon the development of the female organs, producing

pseudo-hermaphroditism (Glynn, 1912 Young, 1937 Vines, 1938) or if exerted after the fifth month of foetal life, adolescent virilism, as Vines's work would suggest adrenal hyperplasia (benign and malignant) basophilic tumour of the anterior pituitary and, of course, disorders of the gonads themselves or of the pituitary-gonadal mechanism. The influence of the adrenal cortex upon sexual characters is far oftener a masculinizing one than the reverse, whether in foetal life or after birth, so that pseudo-hermaphroditism is more likely to occur in genetic females, and virilism in them is much commoner than feminization in males, although adrenal cortical tumours may very rarely have the latter effect, as in the remarkable case described by Simpson and Joll (1938). One may with Maranon and Cawadias, regard the male, among higher animals, as representing a more advanced stage of evolution and as being more stable.

It is, therefore not unlikely that unnatural environmental conditions and stresses, both physical and psychological, of various kinds might affect the ovarian-adrenal relationship and disturb the normal oestrogen–androgen ratio, with the production of some degree of masculinization. This hypothesis is certainly supported by clinical experience and might be explained by the action of stress, primarily on the anterior pituitary and secondarily on the adrenal cortex and ovaries. Selye's important studies on the alarm reaction and the general adaptation syndrome appear to lend further support to this idea (Selye, 1946).

Relative influence of androgens and oestrogens on various tissues

Since the effects of androgens and oestrogens respectively on the surface epithelium of the skin, the hair follicles, and the sebaceous glands now appear clear these structures afford valuable evidence of the preponderating influence of one or the other sex hormone on the skin of a given person, and of any change that may occur in such influence at certain times or in certain circumstances.

Two very important factors, however must be emphasized. One is the relative proportion between the two hormones, the other the sensitivity of the different tissues to hormonal influence. For example, Lawrence and Werthessen (1940) in their studies of the urinary excretion of sex hormones in women with acne (referred to below) conclude that it is the increase in the *ratio* of androgen to oestrogen, rather than a decrease of the latter that is of aetiological importance this is in accord with clinical experience, for many girls and women suffering from acne present no evident signs of ovarian insufficiency There are many observations illustrating the varying degree of tissue sensitivity to hormonal influence, and even of marked differences in such sensitivity of the two sides of the body Weber (1936) has reviewed this subject, pointing out, for example, that bull-dog scalp or cutis verticis gyrata (Unna)—a rare symptom in acromegaly—can be explained only by a localized hypersensitiveness of the skin of the scalp to the pituitary growth hormone he and Atkinson described a case in which the condition was unilateral (Weber and Atkinson, 1928). Bloch (1931), in his illuminating discussion on the pathogenesis of acne vulgaris, concludes that individual differences in susceptibility to comedo formation probably depend upon the follicular apparatus of the skin (the "receptor mechanism") being individually different in its sensibility to the sexual hormones. Bloch (of course) was unaware that in both sexes acne normally results only from androgenic stimulation of the

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follicles, which produces hyperkeratosis of *their mouths and upper portions*, whereas oestrogens have the opposite effect

Furthermore, in their study of acneiform eruptions, *Sulzberger Rostenberg*, and Sher (1934) emphasize the individual hypersensitiveness of the pilo-sebaceous follicles of certain persons to many substances, e.g. to halogens, tar oil, and to the antigens of tuberculosis, syphilis, and certain fungi.

Bourne (1947) has recently elaborated Bloch s conception of tissue-receptors of endocrine influence, and cites the interesting case of a woman whose uterus was completely insensitive to *oestrogen although her vagina responded normally*

Many other examples of individual variations in the response of different tissues to hormonal influence could be given Thus, in only a small percentage of women at or after the climacteric does keratoderma of the palms and soles develop, which presumably indicates hypersensitiveness of these areas to the relative or actual excess *of circulating* androgen that occurs after the menopause. Again in the virile male there is usually a mutual relationship between the activity of the sebaceous glands and the distribution and amount of coarse *hair* but this *is* not always so A man may have intense seborrhoea, acne, a scurfy scalp and seborrhoeic dermatitis, combined with a luxuriant growth of hair on the scalp and only slight hirsuties on the trunk and limbs. Presumably in such a case, whereas the sebaceous glands the infundibula of some of the follicles that do not bear coarse hair and the surface epithelium of the scalp and seborrhoeic areas are sensitive to androgenic stimulation the follicles that in males normally produce coarse hair are relatively irresponsive.

A problem which greatly intrigued Sabouraud, is that of male alopecia, or calvities, with *its distinctive distribution its tendency to affect certain families* severely and to spare others, and its frequent occurrence in varying degree in women, who do not necessarily exhibit other striking signs of virilism. One must presume here that in the majority of males—and in some women with excessive production of androgen—the hair follicles of the temporo-frontal regions and vertex of the scalp react to androgens in exactly contrary fashion as compared with those of other areas that may bear coarse hair and that oestrogens, which have an inhibiting influence on the growth of hair on parts other *than the scalp*, pubic region and axillae, actually stimulate it on the scalp This view is confirmed by the effect of *inunctions of the denuded areas, in female* cases of male alopecia, with an ointment containing an oestrogen Even in advanced cases considerable re-growth of hair may be achieved

The contradictory effects of androgens on the hair follicles of the scalp and on those of the face, trunk and limbs are well illustrated, not only by the majority of virile males, but also by cases of virilism resulting, for example, from a malignant tumour of the adrenal cortex in the female in them the hirsuties of the face and body may be accompanied by male alopecia. When *the source of androgen production* is cut off by successful removal of the tumour there occur re growth of hair on the scalp *and disappearance of the hirsuties*.

Psychological effects of hormonal stimulation

Lastly there is a problem to be considered by the *psychologist, the endocrinologist* and the dermatologist namely to what extent do the qualities of physical

vigour courage, aggressiveness, and initiative depend upon stimulation by androgens? The effects of eunuchism and eunuchoidism on the physical and psychical qualities have been studied by many but care must be taken to distinguish between those of androgen deficiency and those resulting from consciousness of inferiority and impotence Nevertheless, Lister's description of a man suffering from eunuchism due to injury as a weak, whiny sort of person, economically a failure, depressed and melancholy physically feeble and sluggish applies to many and treatment with testosterone may transform such a being, physically and mentally

The interesting experiments of Allee, Collias, and Lutherman (1939), on the peck order in flocks of hens, illustrate the power of male hormone to convert a submissive creature into an aggressive one.

A similar change may be observed in some women after the climacteric, when the diminution of oestrogen may be accompanied by increased androgen production from the adrenal glands.

On the other hand, the dermatologist is familiar with males in whom calvities, strong growth of beard and of coarse hair on the body and limbs, and intensely active sebaceous glands seem to betoken a high degree of androgenic stimulation, but who are lacking in both physical and moral courage. It may well be that in such cases there is an inborn hypersensitiveness of the whole pilo-sebaceous system to testosterone. All that can be said, however from a study of the make up of males and females who come within the normal limits of sex variation, and of such abnormalities as eunuchism, virilism, and masculine sexual precocity is that the quality of androgens is to promote physical and mental vigour aggressiveness, and a strong sexual urge. Oestrogens, on the other hand tend to produce a passive and submissive temperament and a disinclination for violent activities, either physical or constructive. This difference in the effects of the sex hormones on the character of the individual may be illustrated experimentally by administering oestrogens in sufficient quantity to a normal virile male, as in the following case.

Case 1 —A man aged 21 years, vigorous, fond of games and strongly attracted to the other sex, received 200 milligrams of stilboestrol by subcutaneous implantation on account of severe and disfiguring acne. Within a fortnight libido and, indeed, all interest in women were lost. Moreover he became slack and disinclined not only for outdoor games, but for all pursuits involving physical exertion, and his keenness for his work, which was of an active, constructive nature, abated considerably After 5 months, by which time the acne had cleared completely the pellets of oestrogen were removed. Libido quickly returned, together with a desire for feminine company even greater than before the implantation. His inclination for games returned rather more slowly

Whilst it would be a mistake to regard character temperament, and behaviour as being determined solely by functional activity or deficiency of the endocrine glands, it is hardly possible to over-estimate the immense influence that they and the autonomic nervous system, exert upon the physical and psychological attributes of the individual and upon the development of non-specific diseases.

The classical work of Cannon (1939), the beautiful experiments of Cramer (1928) on the thyroid and adrenal glands, and the patient investigations of Selye

(1946) and of many others, afford explanations of how stresses of widely different character—cold, heat, fatigue, infections, and emotional disturbances—may produce temporary and ultimately even permanent tissue damage in various organs through the medium of the endocrine–autonomic system, and may profoundly influence character and temperament

No better illustration of this could be given than that provided by individuals who from infancy suffer from the multiple symptom-complex of so-called allergy —the eczema–prurigo–rhinorrhoea–asthma syndrome. These subjects, as I have pointed out elsewhere (Barber 1929), have been investigated *ad nauseam* by different experts, each with his own view point and method of treatment, but they have been singularly neglected by the endocrinologist Yet a rational explanation of their peculiarities is forthcoming if these are considered in terms of the endocrine–autonomic system for it is clear as Bolten (1925) states, that these patients suffer from a congenital insufficiency of the sympathetic system and of the endocrine glands with accelerator action It seems to be likely that the primary defect is an innate hypofunction of the anterior pituitary which, in turn, would tend to under-action of the thyroid and adrenal glands, and hence of the sympathetic nervous system. The resulting vagotonia accounts for many of their symptoms, and their intolerance of stress (both physical and psychological) their hypotension their tendency to fluid retention (Földes, 1933) the biochemical changes that occur during the exacerbations of their symptoms (Barber and Oriel, 1928) their hypersensitiveness to physical and chemical allergens, and their essentially introvert temperament, all are explicable on the basis of this supposition. Furthermore, many exhibit signs of hypogonadism and puberty in both sexes is often delayed

The thesis cannot be further elaborated here but to conclude these general considerations, the observation of Gley upon the effects of thyroid medication in myxoedema may be quoted *Le genèse et l'exercice des plus hautes facultés de l homme sont conditionnées par l'action purement unique d'un produit de secrétion. Que les psychologues méditent ces faits!*

THE SKIN AND PILO-SEBACEOUS SYSTEM

It is an interesting reflection that although the foundations of endocrinology were laid by physicians and physiologists of Great Britain, the mutual relationship between endocrinology and dermatology has been studied almost exclusively by workers abroad The importance of this relationship is self-evident for cutaneous changes provide a significant part of the symptomatology of most major endocrine disorders moreover sexual differentiation and the waxing and waning of gonadal function are mirrored in the skin and its pilo-sebaceous system Conversely the physical stimuli of light, heat, and cold acting on the skin influence the activity of the endocrine glands and the autonomic nervous system.

With Desaux (1932) one may regard the epidermis as a vast holocrine gland secreting keratin on its surface, and from its invaginations in the dermis, hair nails and sebum It is also quite possible that it may fulfil the function of an endocrine gland The cells of the *rete Malpighii* are rich in cholesterol which is

probably the parent substance not only of the cholic acids of the bile and of vitamin D but also of the hormones and other steroids of the adrenal cortex and gonads (Cameron, 1945). Silberstein, Fellner and Engel (1932) claim to have demonstrated the intracutaneous formation and liberation of an oestrogenic substance as a response to irradiation of the skin.

Certain elements in the dermis form part of the reticulo-endothelial system, which by some is thought to secrete a hormone, reticuline.

The last-mentioned considerations, however are for the most part theoretical, and, as regards the influence of the sex hormones upon the skin and its appendages, we are concerned chiefly with the formation of keratin and horn-fat, and with the activity of the sebaceous glands and apocrine sweat glands.

To Sabouraud the influence of the sex hormones, of sexual evolution, of pregnancy and of the menopause, upon seborrhoea, acne, dandruff seborrhoeic dermatitis, and calvities was clear but naturally the mechanism of their action was unknown. With our present knowledge much can be explained, because two essential facts have been established

(1) that androgens stimulate the surface epithelium and the sebaceous glands, tending to produce hyperkeratosis and seborrhoea

(2) that oestrogens have a contrary action in that they diminish keratinization and the activity of the sebaceous glands.

It cannot be too strongly insisted that the whole problem of the growth and distribution of coarse hair of seborrhoea, of dandruff and of the seborrhoeic eruptions, rests basically on these two facts. It is also now evident that the much disputed role of the triad of organisms that flourish on the seborrhoeic skin is a matter of minor importance. In complete absence of androgenic stimulation of the skin, there is no growth of coarse hair except on the scalp, eyebrows, and eyelids, there is no visible activity of the sebaceous glands, and none of the seborrhoeic eruptions occur Such a condition is very uncommon, but it may be observed in pituitary dwarfism and Simmonds's disease.

Darier's theory of *la kérose*

At this point it is of interest to recall Darier's (1928, 1936) conception of *la kérose* originally published in 1907 which he described as a chronic morbid state of the skin, characterized clinically (1) by a dirty yellow *bistrée* or greyish colour (2) by an accentuation of the pilo-sebaceous orifices (3) by slight thickening of the integument The histopathology reveals (1) a slight diffuse hypertrophy of the *stratum corneum* with a tendency to fine desquamation, and a modification of its fatty content (2) hyperkeratosis of the pilo-sebaceous orifices.

For Darier *la kérose* provided the necessary substratum for the development of pityriasis simplex and steatoides, of seborrhoea, of certain forms of alopecia and hypertrichoses, of acne, and of the various forms of seborrhoeic dermatitis (*eczématides*). Its characteristics are, in fact, those of what is commonly termed the seborrhoeic skin which I have described elsewhere (Barber 1929).

Darier remarks that the topographical distribution of *kérose* is both diffuse and regional. It may be summarized as follows scalp centre of the face,

It has also been shown (Edwards *et al.*, 1941) that in eunuchs and castrates the characteristic pallor of the skin can be changed to a darker and ruddier hue by injections of testosterone propionate. This is due to a marked increase in the vascularity of the skin and in the formation of melanin and melanoid. Moreover carotene is present in excess in the skin of castrates, but is reduced to normal by such treatment.

Stimulation by oestrogens

The effects of oestrogens upon the skin may be studied most conveniently in women, at and after the climacteric, who present various changes clearly or presumably due to androgenic influence. Similar observations may be made on adolescent girls and women suffering from seborrhoea, acne, and seborrhoeic dermatitis. The most remarkable illustration of their effects, however, is provided by the administration of oestrogens in sufficient dosage to males with active seborrhoeic eruptions. During the past few years, P. M. F. Bishop and I have treated some severe cases of acne, with the indurated and cystic lesions that result in disfiguring scars, by subcutaneous implantation of pellets of an oestrogen—in most cases stilboestrol.

The effects on the skin may be summarized as follows.

(1) The activity of the sebaceous glands is remarkably diminished.

(2) The pilo-sebaceous orifices are reduced in size and are no longer easily visible to the naked eye.

(3) The slight hypertrophy of the *stratum corneum* disappears, and the surface of the skin becomes smooth and delicate, like that of a child.

(4) With the diminution of the seborrhoea, the hair of the scalp becomes drier and fluffy as in the normal or pregnant female.

(5) Dandruff ceases to form and may disappear without local treatment of the scalp.

(6) The comedones shrivel, become desiccated, and may easily be picked out of the follicles with the finger nail.

(7) Pustules subside, and the indurated and cystic lesions gradually involute.

(8) The growth of coarse hair on the face diminishes in vigour so that daily shaving may be hardly necessary.

The same effects may be obtained by the oral administration of stilboestrol, but in my experience unexpectedly large doses must be given for a considerable time. Similarly local inunction with an ointment containing a synthetic oestrogen in sufficient concentration has a remarkable effect on dandruff and on the surface hyperkeratosis. I have not employed it in acne to a sufficient extent to judge of its efficacy.

DISTRIBUTION AND GROWTH OF COARSE HAIR

Aristotle, among his 'Problems' remarked that children, women, and eunuchs do not become bald. He was referring, of course, to the common baldness of men, or calvities, and not to loss of hair from other causes, such as alopecia areata. Sabouraud, as is mentioned above, emphasized the influence of the sex glands upon the growth and distribution of coarse hair and the activity of the sebaceous glands,

particularly the nose and naso-labial folds forehead and temples, chin, and nape of the neck the presternal and interscapular regions also frequently the shoulders, pubis, genitals, internatal cleft and main joint flexures. The areas usually spared are the front of the neck, the extensor surfaces of the limbs, the buttocks, and the forearms and legs as a whole. He points out that this distribution is more or less the inverse of that of ichthyosis

Stimulation by androgens

It is now clear that the basic factor upon which Darier s *kérose* and its various manifestations depend is stimulation of the epidermis, hair follicles and sebaceous glands by androgens, derived either from the male gonad or from the adrenal cortex.

The *presumptive evidence* for this assertion is provided (1) by a comparison of the skin of the virile seborrhoeic male with that of the ultra feminine female (2) by studying the skin of cases of frank virilism e.g. due to hyperplasia or tumour of the adrenal cortex, or to Cushing s syndrome (3) from observations on the various changes that occur in the skin of some women at or after the climacteric, or earlier when, for one reason or another the oestrogen–androgen ratio is abnormal

Now however we have the *direct experimental evidence* afforded by the administration of androgens to females, eunuchs, male castrates, and eunuchoids, and of oestrogens to seborrhoeic males and to females whose skin betrays androgenic stimulation by reason of seborrhoea and its complications, or of certain menopausal changes The effects of androgens and oestrogens on the skin may be obtained by subcutaneous implantation intramuscular injection or oral administration or by absorption through the buccal and vaginal mucous membranes and the skin The choice between these various methods is decided by the nature of the individual case. Administration of androgens is seldom employed in the treatment of female disorders, and Hamblen (1945) now holds the opinion that androgenic therapy regardless of what may be its supposed indication, always is contra indicated in the treatment of the female Nevertheless, testosterone propionate and methyl testosterone have been given for certain menopausal symptoms (particularly metrorrhagia) for metropathia haemorrhagica, and for some other conditions, such as nodular mastitis When large doses of testosterone propionate (more than 500 milligrams per month) are unjustifiably administered acne and hirsuties may be produced in addition to enlargement of the clitoris and changes in the vagina and endometrium

It is, however in the treatment of eunuchs, eunuchoids, and male castrates that the effects of androgens have been chiefly studied. Hamilton s observations upon the influence of such treatment in provoking activity of the sebaceous glands and the development of acne are reviewed below (Hamilton 1941) Apart from this, there occur an increase in pubic and axillary hair and a growth of coarse hair on the face trunk, and limbs

Such results illustrate the stimulating action of androgens upon sebaceous activity, and upon the formation of keratin in the follicles that are capable of producing coarse hair and at the ostia of those that are not

seen), the inner and upper portions of the thighs, and the extensor surfaces of the limbs.

In the most feminine type of woman, on the other hand, the hair on the head is luxuriant, there is no coarse hair on the face and limbs, and on the trunk only in the axillae and pubic regions. The upper border of the hair on the pubis is a horizontal line like the base of an inverted triangle, whereas in the male the hair extends irregularly upwards along the *linea alba*.

Although some degree of calvities is a normal male characteristic, and although, as a rule, the earlier it appears and the more relentless its progress, the stronger the growth of hair on the face, body and limbs, nevertheless there would seem to be an hereditary factor In certain families the males are prone to early and rapidly progressive baldness in others this tendency is absent, although the males may be exceptionally virile and hirsute. Fantham (1924) has published the pedigree of a family in which in all the males complete calvities developed at a very early age. On the other hand, in my own family not a single male out of 30 in 4 generations became bald, although some of these had an unusual degree of hirsuties. Cockayne (1933), however rightly remarks that caution must be exercised in accepting the view that the liability to baldness can be transmitted either as a sex linked recessive or by a gene in the Y-chromosome

The hormonal control of normal hair growth in the two sexes

In considering the growth of hair in both sexes a distinction must be made between that on the scalp lids, and eyebrows, and that on the pubic and axillary regions, face, trunk, and limbs. It has been assumed that the latter which does not normally appear before puberty is dependent upon anterior pituitary and gonadal functions. In women, however and to a less extent in men, the growth of pubic and axillary hair would seem to be a function not of the gonads but of the adrenal cortex.

The evidence for this has been discussed by Albright, Smith, and Fraser (1942) in a description of their syndrome of primary ovarian insufficiency with decreased stature, by Wilkins and Fleischmann (1944) in their study of similar cases ("ovarian agenesis") and by Kepler Peters, and Mason (1943) in connexion with Addison's disease.

In women the 17-ketosteroid excretion is an index of adrenal cortical function (Fraser *et al* 1941). It rises at puberty indicating the increased adrenal activity that accompanies that of the ovaries hence the appearance of pubic and axillary hair at this time might be due to either In primary ovarian insufficiency moderate amounts of this hair are present as a rule the quantity is less than normal, as is the excretion of 17-ketosteroids.

In pituitary deficiency dwarfs, in whom both the adrenal cortices and ovaries are atrophied, there is no axillary or pubic hair Similarly in adult women the hair disappears or greatly diminishes in panhypopituitarism (Simmonds's disease, pituitary cachexia), in Addison's disease, in hypothyroidism, and in extreme old age, when, as Severinghaus has shown (1944) degenerative changes take place in the chromophile cells of the anterior pituitary In all these cases the excretion of 17-ketosteroids is extremely low or is absent.

and he instituted an enquiry among the harems of the East in order to test Aristotle's assertion on the immunity of eunuchs to baldness, confirming its truth (Sabouraud 1932)

He also made the significant observation that with very rare exceptions, oily seborrhoea of the scalp and loss of *hair of male type cease from the beginning of* the third month of pregnancy only to return as before within 2 or 3 months after parturition Sabouraud offered no explanation of this *influence of pregnancy on* the hair follicles and sebaceous glands of the scalp, but we know now that after an initial fall (less than during the menstrual period) the *oestrogen content of the blood* progressively rises from the end of the second month of gestation (Mazer and Goldstein, 1932) to a level that, just prior to term, is considerably higher than that of the premenstrual phase. Although much of the oestrogen formed during pregnancy from the placenta is excreted in the urine, there is nevertheless a veritable oestrogen plethora which accounts for the hyperplasia of the breasts, the erection of the nipples, and the increased pigmentation of the areolae and of the *linea alba*. That these symptoms are the result of stimulation by oestrogen is revealed by the fact that they may be provoked experimentally *in both sexes* by sufficient dosage of natural or synthetic oestrogens.

It should be noted *that the time of their appearance corresponds approximately* to that of the diminished activity of the sebaceous glands and of the arrest of the alopecia i.e. *towards the end of the second month* when the oestrogen-content of the blood begins to rise. From that time onwards, almost invariably the scalp hair and complexion of the seborrhoeic pregnant female progressively improve. As Sabouraud (1932) so graphically put it *A quelques exceptions près fort rares la femme séborrhéique ne montre jamais de plus jolis cheveux que pendant ses grossesses Le cuir chevelu cesse d'être gras le cheveu n'est plus collant et l'alopécie s'arrête Même chez des femmes qui perdaient des cheveux par centaines la chute s'interrompt au deuxième mois et demi de la grossesse pour ne reprendre que deux mois ou deux mois et demi après les couches* In addition, dandruff diminishes or disappears, the complexion becomes smooth and no longer greasy and comedones and acne pustules cease to form

That this temporary transformation like the enlargement of the breasts and the *increase of pigmentation depends upon the increase of available oestrogen during* pregnancy cannot be doubted, and it is interesting to compare these changes with *those already described as resulting* from adequate oestrogenization of the male.

Distribution of coarse hair in males and in females

We must now discuss the distribution of coarse hair in the two sexes and consider the hormonal control of its growth. After puberty the virile male tends gradually to lose the hair on the temporo-frontal regions and vertex of the scalp, and to grow coarse hair on the face, trunk and limbs. In some men the hirsuties on the body and limbs may be so profuse as to be almost universal—I have seen this with advanced calvities in a sexually precocious boy aged 13 years—but the areas most characteristic for comparison with females are the front of the chest, where the hair forms a kind of breastplate, the *linea alba* or umbilical-pubic line the sacro-coccygeal region (on which a thick tuft of hair the *satyr's tail* may be

the seborrhoeic triad, but *Staphylococcus pyogenes albus*, *Staph. aureus* and *Staph. citreus* may also be responsible for eruptions that are associated with the seborrhoeic state—for example pustular acne, boils and sycosis.

It is generally agreed that the seborrhoeic triad are normal habitants of the skin, and that in certain conditions they are observed in a state of very active growth. The problem for discussion is to what extent such activity is of pathogenetic significance. The more exact knowledge that we now possess, concerning the influence of the sex hormones upon the *stratum corneum* and the sebaceous glands, has to some extent simplified it: we must regret that Sabouraud did not live to understand fully the clinical facts that he had observed.

With his views I am still substantially in agreement, although I no longer believe that the acne bacillus is the cause of comedones, and have never considered its growth to be the stimulus responsible for seborrhoea (as Sabouraud originally suggested), nor as playing any part in the development of calvities. In his later writings, Sabouraud (1932) himself, in discussing the problem of calvities, remarks: *La microbiologie en constatant le développement banal de sa flore constante et exclusive pose un point d'interrogation plutôt qu'elle ne résout le problème. Et c'est, à mon avis, l'étude endocrinologique qui contribuera le plus à le résoudre ou à résoudre au moins une part des inconnues qu'il garde encore. Et même en admettant prouvé le rôle des glandes endocrines, la délimitation des surfaces chauves demeure rafi encor assez mystérieuse.*

I agree with Goldsmith (1936) that the bacteriology and mycology of the seborrhoeic skin need further systematic investigation along the lines so patiently pursued by Sabouraud. In the meantime my own views are as follows:

(1) The pityrosporon of Malassez

The evidence that this organism is the cause of pityriasis simplex (dandruff) seems to me convincing. As Sabouraud (1904, 1932, 1936) pointed out in his original studies, examination of vertical sections through the scales shows that it multiplies in the *stratum corneum* in the same position and fashion as does *Microsporon furfur* in pityriasis versicolor. This observation was confirmed by Whitfield (1911).

Experimental investigations with this organism have been handicapped owing to the difficulty of cultivating it. MacLeod and Dowling (1928) inoculated cultures of an organism, which had long been claimed to be the pityrosporon by W. O. Garner, on seborrhoeic and non-seborrhoeic skins, and on the former produced apparently typical figurate patches of seborrhoeic dermatitis. Moore *et al.* (1936) made similar claims with an organism which they termed *Pityrosporon ovale*. Dowling, however, now believes, with Ota and Huang (1933), that Garner's organism is a monilia which grows freely on some skins but not on others.

Personally I doubt whether any of the cultured organisms are identical with the pityrosporon, but agree with Sabouraud and with Whitfield that the latter is almost certainly the cause of true pityriasis simplex, which may spread from the scalp as dry furfuraceous flakes with no underlying inflammatory reaction in the skin to other parts. This is often well seen, for example, at the openings of the external auditory meatuses, in the retro-auricular spaces, on the forehead, on the sides of the neck, and on the posterior parts of the cheeks.

That ovarian activity is not of importance in influencing the growth of pubic and axillary hair is shown by the fact that after a normal or artificial menopause it undergoes little change, except that it becomes uncurled.

In Addison's disease, ovarian function may be, for a time at least, perfectly normal yet the pubic and axillary hair is completely absent or very scanty as in the cases described by Albright, Smith and Fraser (1942) and by Kepler Peters, and Mason (1943) In those of primary ovarian insufficiency described by Albright *et al* and by Wilkins and Fleischmann (1944), administration of oestrogen markedly increased the growth of pubic and axillary hair This was probably due to stimulation of the adrenal cortex via the pituitary by oestrogen. On the other hand in panhypopituitarism (pituitary dwarfism Simmonds's disease) oestrogenic therapy has no effect on the hair although Wilkins and Fleischmann describe the case of a female pituitary dwarf aged 22 years, with infantile breasts, vagina and uterus and no pubic and axillary hair in whom under treatment with stilboestrol 1 milligram and methyl testosterone, 25 milligrams daily a considerable growth of pubic hair resulted and the breasts, vagina, and uterus developed normally When the methyl testosterone was omitted and stilboestrol given alone, all the pubic hair fell, but it reappeared upon resumption of the male hormone.

These observations seem to prove that *in females* the stimulus to the normal growth of pubic and axillary hair is androgenic and is independent of ovarian integrity the androgen being derived from the adrenal cortex.

In males castration of adults leads to a diminution of hair on the pubic and axillary regions. That on the pubis reverts to the feminine configuration. Castration before puberty does not prevent the development of pubic and axillary hair but again on the pubis it is of feminine type

To sum up in females the growth of pubic and axillary hair is apparently promoted and maintained by an androgenic hormone produced in the adrenal cortex. Hence the hair is present, although usually not profuse, in castrates and in cases of ovarian agenesis, but is completely absent in pituitary dwarfs and in Simmonds's disease and is usually so or very scanty in Addison's disease.

In males, growth of pubic hair of feminine configuration and of axillary hair occurs in the absence or atrophy of the testes, and to this extent is then also presumably dependent upon adrenal androgen As in females, it is absent in panhypopituitarism

It would seem, therefore, that what may be called a neutral growth of hair strictly confined to the pubic and axillary regions, occurs in both sexes despite lack of the gonadal hormones, from whatever cause it may arise, provided that the adrenal cortex is functionally intact it is thus dependent upon an androgenic substance of adrenal origin

SEBORRHOEIC ERUPTIONS

The role of the micro-organisms found actively multiplying in the so-called seborrhoeic eruptions is still disputed The pityrosporon of Malassez, the acne bacillus, *Corynebacterium acnes* and *Micrococcus cutis communis* may be termed

The terminology of seborrhoeic eruptions

The term, eczema seborrhoeicum, has rightly been discarded by most dermatologists, but the objection to it is not, to my mind, because the word, eczema, is best reserved for a certain type of epidermal reaction that is primarily amicrobial, but on account of the epithet, seborrhoeic. The same objection applies to the terms, seborrhoeic dermatitis and seborrhoeide, which are now unfortunately in current use, for although this type of eruption is commonly associated with seborrhoea, it is essentially due to diffuse infection of the *stratum corneum* and has no necessary connexion with the pilo-sebaceous follicles. I prefer Sabouraud's title pityriasis steatoides for this at least indicates its relationship to pityriasis simplex, although the epithet, steatoides, is misleading, since as Sabouraud himself insists, the apparent greasiness of the scales is due not to fat but to the presence of dried serum lying between the strata of parakeratotic horny cells. By staining with osmic acid it may indeed be shown that these greasy scales (*'squames croutes'*) contain less fat than do those of the normal *stratum corneum*.

Darier proposed the term *eczématide* as an alternative to seborrhoeic eczema and seborrhoeide, and described three main forms of eruption (1) *eczématides figurées* (medio-thoracic seborrhoeide or flannel-rash *corona seborrhoeica*) (2) *eczématides pityriasiformes* and (3) *eczématides psoriasiformes* The histological differences between these last and true psoriasis have been analysed in masterly fashion by Civatte (1924).

Darier rightly insists that the association of this group of eruptions with seborrhoea, though usual, is inconstant, and points out that, although their histopathology resembles that of eczema, clinically they differ from true eczema in four respects (1) their habitual dryness, (2) the sharp definition of their borders, (3) their long persistence without change in appearance, and (4) their ready response to treatment by certain topical applications. He remarks that their characters suggest a dermatosis due to local microbial infection, occurring on a special *terrain—kérose* with or without an accompanying seborrhoea—and eczematoid in type, but with less serous and cellular exudation. In certain circumstances they may become impetiginized from superadded pyococcal infection or frankly eczematized. Whilst admitting the convenience of Darier's term—*eczématide*—as denoting the eczematoid nature of the eruption, I prefer to reserve the suffix -ide for dermatoses that result from allergic cutaneous reactions to antigens reaching the skin or subcutaneous tissue through the blood-stream (tuberculides, syphilides, leprides, trichophytides, streptococcides), and not from local infections of the skin itself

At all events, Sabouraud and Darier were agreed as to the absurdity of the terms seborrhoeic dermatitis or seborrhoeide they are almost as fallacious as is Hebra's conception of seborrhoea sicca which is a contradiction in terms and should long since have been expunged from dermatological nomenclature.

For this reason I would advocate Sabouraud's title, pityriasis steatoides, for want of a better alternative. His descriptions of the transition, clinically and histologically from simple dry dandruff to pityriasis steatoides of the scalp and other parts should be read in the original (Sabouraud, 1904 1932, 1936). They are a model of clarity

An important point is that *in the purest form of pityriasis simplex, this organism is the only one to be found microscopically in a state of active growth.*

Effect of sex hormones on the pityrosporon

Assuming, then that it is the cause of dandruff we must consider the interesting effects of the sex hormones upon its growth. Despite opinion to the contrary it may be said that true dandruff is very rarely seen on the scalp of a child before the age of 9 or 10 years, i.e. the pre-pubertal age when the awakening of the sebaceous glands commonly begins. Like acne, it is frequently observed in both sexes but more so in boys, and, as a rule, the greater the tendency to seborrhoea and acne, the more severe the dandruff. In some girls, and in a few boys who *retain their childhood's complexion* it is completely absent. I know of no information as to whether or not it is ever present in eunuchs and eunuchoids.

From what has already been said however it would seem likely that, for the active growth of the pityrosporon to occur in the *stratum corneum* the presence of circulating androgen is essential. That oestrogens inhibit its growth is indicated by the observations already cited. In both sexes their administration in sufficient dosage diminishes or abolishes dandruff without topical treatment and local applications of an ointment containing them are rapidly effective moreover *during pregnancy dandruff may disappear completely.*

These observations recall the influence of puberty upon the growth of *Microsporon audouini* the presence of which, except very rarely ceases spontaneously in both sexes towards the age of 15 years. Whether this is due directly to an inhibiting action of the sex hormones, as Hruszek's (1934) experiments, perhaps, suggest or to the change in the composition of the epidermal lipoids that Sannicandro (1934) has described (increase of cholesterol esters), or to an alteration of the *p*H in the superficial layers of the epidermis, is uncertain.

(2) *Micrococcus cutis communis* (*Coccus butyricus* polymorphous coccus of Cedercreutz *Morococcus* of Unna)

This organism has been confused with Welch's *Staphylococcus epidermidis albus* and other strains of the *Staph. pyogenes albus* but it differs from them in never liquefying gelatin. Cultures of it on agar emit a smell of butyric acid.

It has a historical interest in that upon it was based Unna's entire conception of *eczema seborrhoeicum*. His original observations were correct and of importance, because he noted the transformation of pityriasis simplex, in which he found only the pityrosporon (erroneously christened by him the "bottle-bacillus"), into pityriasis steatoides, which was the earliest stage of his seborrhoeic eczema, and attributed this to the polymorphous coccus, which he named *Morococcus*. Furthermore, to him belongs the credit of identifying seborrhoeic dermatitis of the back and chest ("flannel-rash") and of the eyebrows and naso-labial folds with pityriasis steatoides, and of describing the corona seborrhoeica.

Unfortunately on this sound basis, partly owing to ignorance of bacteriological technique he erected a fantastic superstructure of the grossest errors, in that even primarily amicrobial eczema (whether of endogenous or exogenous origin) and psoriasis were included in his eczema seborrhoeicum!

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for this. Under the influence of certain factors, however which are discussed below a much more inflammatory variety of seborrhoeic dermatitis involving the same areas, may supervene, accompanied by intense serous oozing and complicated by boils, abscesses, and sycosis. This severe variety is clearly due, I think, as cultures indicate to a superadded infection with *Staphylococcus aureus*

Lastly a rather different complication may result from secondary invasion with *Streptococcus pyogenes longus* particularly on the scalp and in the retro-auricular spaces and folds of the pinnae, as described by Sabouraud (1932, 1936). Fissures form in the depths of the folds, and on the scalp the *fausse teigne amiantacée* so commonly present in association with primary streptococcal intertrigo of the retroauricular folds, may be seen

To sum up the views expressed

(1) The pityrosporon is probably the cause of a non-inflammatory exfoliation of horny cells on the scalp or elsewhere—pityriasis simplex

(2) the transformation of this into pityriasis steatoides (simple form of seborrhoeic dermatitis ") is due to a secondary invasion of the *stratum corneum* by the *Micrococcus cutis communis* (*Coccus butyricus Morococcus*)

(3) a more inflammatory variety of seborrhoeic dermatitis may result from superadded infection with other more virulent strains of staphylococcus—usually *Staph. aureus*—and be complicated by invasion of the follicles, producing boils and sycosis

(4) similarly invasion by *Streptococcus pyogenes longus* may occur

ACNE VULGARIS

I do not propose to discuss the aetiology of the eruptions to which the term, acne, is applied other than *acne vulgaris seu juvenilis* Therefore I shall not consider any of the following forms *acne necrotica acne artificialis* provoked by halogens, oil, tar etc. cheloid acne *acne conglobata* of which *perifolliculitis capitis abscedens et suffodiens* (Hoffmann) is probably a variety localized to the scalp.

The literature dealing with the aetiology bacteriology and treatment of acne vulgaris is so vast that no attempt will be made to review it. Much of it is contradictory and opposed to conclusions derived from clinical and experimental experience. As with seborrhoea, which is the necessary precursor of acne (whether this occurs in adolescence, in the prime of life, or at the climacteric, or whether it be provoked experimentally), the essential fact, which must dominate all speculations concerning aetiological considerations, is that androgens favour its development whereas oestrogens inhibit it. Without androgenic stimulation of the pilo-sebaceous follicles acne does not occur and as is mentioned above, even in virile males sufficient dosage with oestrogen will cause the lesions to involute. As with other seborrhoeic eruptions, however other factors (reviewed below) which aggravate an existing tendency come into play

The lesions of acne

The epithet polymorphous as applied to acne, is justifiable, for the lesions that constitute a severe eruption may be of various kinds. They are as follows

Pityriasis simplex and steatoides

We are concerned rather with the question of the organisms responsible. There is, I think, general agreement on the close relationship between these two forms of pityriasis—simplex and steatoides—and on the infective nature of the latter concerning which three alternative views present themselves.

(1) That the pityrosporon itself is capable of exciting the mild inflammatory response represented by the simple forms of pityriasis steatoides.

(2) That the transition from pityriasis simplex to pityriasis steatoides is due to the active growth of the *Micrococcus cutis communis* being superadded to the existing infection of the *stratum corneum* by the pityrosporon—the view held by Unna and by Sabouraud

(3) That one cannot with certainty incriminate any particular organism or strain of staphylococcus this was the opinion of Darier who held that neither by direct examination of the scales nor by culture could one decide which organisms were pathogenic and which were saprophytic or accidentally present

With regard to (1) it is possible that the pityrosporon like other organisms of the monilia group, might provoke an inflammatory reaction as well as the non-inflammatory exfoliation of the horny layer that produces simple dandruff but we have as yet no definite proof of this, and it is significant that, in pityriasis steatoides, actively growing staphylococci are always found to accompany it.

With regard to (2) and (3) I hardly care to express an opinion without the support of further systematic investigations, but would tentatively suggest the following compromise between the two If we regard the pityrosporon as being the cause of pityriasis simplex on the scalp and elsewhere, it seems to be likely that it might, in certain circumstances, favour active invasion of the *stratum corneum* by other organisms which may be present on the skin namely various strains of staphylococci and a streptococcus. This view is certainly supported by clinical observations. Sabouraud has described in detail the gradual transformation of the dry flaky scales of pityriasis simplex on the scalp into the more adherent greasy and confluent scales of pityriasis steatoides he showed that this change is due to serous exudation into the *rete Malpighii* very slight and hardly visible at first after removal of the scales, but increasing and being accompanied by slight reddening of the surface. As in eczema, this serous exudate coagulates, and with leucocytes, becomes imprisoned between the layers of parakeratotic horny cells, thus forming the greasy scales.

The same transformation from pityriasis simplex to pityriasis steatoides may be observed elsewhere, e.g. on the forehead in the meatuses and folds of the pinnae, in the retro-auricular spaces, on the eyebrows and margins of the lids, in the naso-labial folds, on the moustache and beard on the presternal and inter scapular regions, and in the joint flexures. This constitutes the simplest form of seborrhoeic dermatitis and is characterized by the slightness of the inflammatory reaction and serous exudation. It seems probable that the original observations and conclusions of Unna and of Sabouraud were correct and that it is the invasion of the *stratum corneum* (already infected with the pityrosporon) by the *Micrococcus cutis communis* an organism of low athogenicity that is responsible

the follicle, causing retention behind it of the sebaceous matter which contains myriads of microbacilli. Unna also proved that its dark colour is due to oxidation of keratin, which accounts, too, for that observed in severe ichthyosis (ichthyosis nigricans) and in a cutaneous horn.

Sellenbach-Keller (1930) pointed out that the development of comedones occurs *pari passu* with that of the pubic and axillary hair and this observation was confirmed by the meticulous investigations of Bloch (1931) on 4 191 children of both sexes between the ages of 6 and 19 years. Their conclusions are substantially the same, namely that the formation of comedones is the consequence of the physiological action of the gonads and is analogous to the development of sexual hair As is shown above, however the growth of pubic and axillary hair in both sexes is dependent upon androgenic stimulation of the follicles, and the same is obviously true of coarse hair on the trunk and limbs and on the face (except for the eyebrows and eyelashes), occurring normally in males and abnormally in females.

Logically therefore, one may conclude that comedones also result from the stimulation to keratinization exerted by androgen, most of which is doubtless derived from the gonads in males and from the adrenal glands in females. As is mentioned above in the latter there is a rise in the excretion of 17-ketosteroids at the time of puberty indicating the increased adrenal activity that accompanies that of the ovaries. As one would expect, the incidence of comedones and the frequency and severity of polymorphous acne are higher in boys than in girls, and Bloch's figures confirm this. A further correlation between the development of coarse hair and of comedones is observed in some women at the menopause, and in cases of virilism due to adrenal hyperplasia or tumour in pituitary basophilism, and in sexual precocity in males.

Hormonal factors in acne

Hamilton (1941), who has contributed an admirable review of the aetiological factors responsible for acne vulgaris, by his observations on the effects of treating cryptorchids, eunuchoids, and adult castrates with injections of testosterone propionate, has afforded us conclusive experimental proof of the influence of androgen on sebaceous activity and the formation of comedones, and of the papules and pustules of acne Of 31 boys and young men thus treated for cryptorchidism, 19 of whom were under 12 years of age, in 22 comedones developed in varying degree The first effect observed on the skin was increased sebaceous activity with subsequent comedo formation, chiefly on and around the nose, the early localization so often seen at puberty

An illustrative case recorded by Hamilton, was the following.

Case 2 —The patient was a unilateral cryptorchid up to the age of 35 years, when the descended testicle was removed and severe castration symptoms resulted. He had had acne in adolescence, but none for 13 years prior to the operation, which was followed by great reduction in sebaceous secretion, the skin becoming smooth and dry as in eunuchs 10 months later he was given mock treatment without effect on the skin Administration of testosterone propionate in adequate dosage was followed within 10 days by oiliness of the skin, particularly around the nose. This disappeared when treatment was withheld. On resumption of the treatment there

(1) comedones, which may be double (2) inflammatory papules or pustules formed in connexion with follicles containing comedones (3) superficial pustules at the mouths of follicles without comedones (4) deeper indolent, and often painful lesions (5) follicular sebaceous cysts (' *tannes* in French) which result from blocking of a pilo-sebaceous follicle by a large comedo and contain a pasty substance, smelling of butyric acid and consisting of keratinized epidermal cells, fat, crystals of fatty acids, soaps and cholesterol, which can be expressed through the umbilicated opening (6) mucoid cysts, *containing a gelatinous matter and due to cystic* degeneration of a long-obstructed sebaceous gland.

Of these various lesions those that truly constitute acne vulgaris are (1) the comedones (*acne punctata*) (2) the inflammatory papules or pustules formed around comedones (*acne papulata et pustulosa*) (3) the deeper nodular lesions (*acne indurata*) The banal superficial pustules at the mouths of follicles without comedones, although very common in acne, occur at times in most persons they are due to *Micrococcus cutis communis* or to *Staphylococcus albus*

The bacteriology of acne vulgaris has been disputed since, in 1893 Unna first described the true nature of the comedo and found in it constantly the acne bacillus, which he failed to cultivate. The chief argument has been concerned with the rival claims of the acne bacillus and of staphylococci to be the cause of the superficial and deep inflammatory papules and pustules. Goldsmith (1936) throws doubt on the claims of either organism particularly (as the result of his own investigations) on those of the staphylococci. He also states that it has never been possible to produce acne lesions in man by rubbing in cultures of the acne bacillus Fleming (1909), however claimed to have produced pustules by rubbing into the forearm of a patient with acne a broth culture of the organism, but he failed to do so *in one who was free of acne* Sabouraud on the other hand, held that the superficial type of pustulation in acne was staphylococcal.

Of more interest are the deeper indurated lesions, which may persist with little change for weeks, but tend eventually to soften and fluctuate from them a liquid and often blood-stained pus may be expressed followed sometimes on further pressure by a semi-solid gelatinous mass. These indolent nodules were described in detail by Gilchrist, who found histologically that they were made up of masses of cells, including giant cells, plasma cells, lymphoid and connective tissue cells, polymorphonuclear leucocytes, and large phagocytes. Some of the giant cells contained acne bacilli. Unna was the first to point out that in the nodules only these bacilli were found, and Sabouraud confirmed this, both agreeing that they were *often seen engulfed by phagocytes.* Western, in such lesions, found only bacilli and no staphylococci. Ramel's claim to have demonstrated that they are *of tuberculous origin has not been accepted* and there is a good case for their being a special type of tissue reaction to the acne bacillus.

Nature of the comedo

Unna Sabouraud and Whitfield all held that the comedo is a cystic reaction of the horny cells to the presence of acne bacilli multiplying in the infundibulum of a *pilo-sebaceous follicle, and at one time I accepted this view* As Unna first showed the comedo results from hyperkeratosis at the mouth and upper part of

stimulate keratinization of the surface of the skin and in the pilo-sebaceous follicles, and active secretion of the sebaceous glands, but they further appear to favour the growth of the seborrhoeic triad of organisms, whereas oestrogens have exactly contrary effects.

Apart from inherited and individual predisposition, which may determine the susceptibility of the epidermis and follicular structures to hormonal influence (Bloch's "receptor mechanism"), the tendency to the development of active seborrhoeic eruptions in both sexes probably depends upon *the relative proportions* of circulating androgens and oestrogens. Some of the evidence in favour of this view may be recapitulated and summarized as follows

(1) All these eruptions are commoner and tend to be more severe in males than in females.

(2) The eunuch, the eunuchoid and the male castrate are free from them, as is also the effeminate type of man, as a rule on the other hand, they are very common and in some degree may be considered to be physiological in virile males, particularly during adolescence. In the female they are apt to occur when from some cause (emotional disturbances, stress, or actual local or general disease) ovarian deficiency develops, and they are common in even slight cases of virilism.

Lawrence and Werthessen (1940), in their study of the excretion of oestrogen and androgen in the urine of 8 normal women and 8 female patients with acne, found a decrease from the normal in the excretion of urinary oestrogen by those with acne, but no significant change in excretion of androgen. (The material did not, of course, include cases of virilism.) The androgen-oestrogen ratio, expressed as

$$\text{Ratio} = \frac{\text{Androgen}}{\gamma \text{ oestrone equivalent}}$$

averaged 2·46 in the normals, and 6·67 in the cases of acne. They conclude that a disturbance of the androgen–oestrogen ratio is a significant aetiological factor in acne

(3) As I have pointed out elsewhere (Barber 1946) many women who are approaching, or have arrived at, the climacteric afford as favourable an opportunity of studying the development and evolution of the seborrhoeic eruptions—and particularly of seborrhoeic dermatitis—as do the pre-pubertal child and adolescent. This is not surprising, since, with diminishing ovarian activity and in some cases an actual increase in the formation of androgen from the adrenal cortex, the oestrogen–androgen ratio is altered (Goldzieher 1939). Frequently these patients have had acne severe dandruff, or seborrhoeic dermatitis in earlier life, which has disappeared after marriage and child-bearing in others these may develop at the menopause for the first time.

As a rule, the first symptom is increasing scurfiness of the scalp, and the dry scales of pityriasis simplex may be observed elsewhere. Later the more inflammatory seborrhoeic dermatitis may supervene and spread downwards to the following parts the retro-auricular spaces the meatuses the eyelids, naso-labial folds, and chin the sides of the neck the mediothoracic regions the axillae the submammary folds the umbilicus the pubic region, groins and internatal cleft. In some cases the inflammation may be severe with much serous oozing.

appeared a widespread eruption of comedones and acne papules on the back and face, which subsided when the injections were omitted. After further effective treatment the acne reappeared and became more widespread, but again it markedly diminished after temporary cessation of the treatment for a week. It relapsed on resumption, but faded rapidly when finally the injections were discontinued, and the seborrhoea ceased A total of 16,170 milligrams of testosterone propionate was given over a period of 77 weeks

Of 9 eunuchoids and castrates treated by Hamilton, acne of considerable severity developed in 7 He notes that in a castrate, who had had acne severely in adolescence, androgenic therapy was followed by a more intense eruption than was observed in the others. Three of Hamilton's patients stated that excess of carbohydrates and chocolate quickly provoked an increased number of inflammatory papules.

By the courtesy of Dr Peter Bishop I have observed a eunuchoid patient under his care whom he had treated by subcutaneous implantation of testosterone. In this case, also comedones and acne papules and pustules developed on the face and on the central parts of the back and chest.

Three points of interest should be noted in Hamilton's observations. (1) That, as regards the effect on the pilo-sebaceous follicles, treatment of cryptorchids, eunuchs, and castrates with testosterone creates an artificial puberty and the same march of events is noted first the awakening of sebaceous activity which begins as at puberty on the central parts of the face secondly the formation of comedones at the ostia of some of the follicles thirdly in some cases the appearance of acne papules and pustules (2) The second point is that in the castrate, who had had acne severely in youth, under the influence of testosterone a more intense eruption developed than in others who had not so suffered thus illustrating the individual differences in the susceptibility of the follicles to hormonal influence that Bloch postulated when he referred to variations in the receptor mechanism (3) The third point is that excess of carbohydrate and chocolate may aggravate an artificially produced acne as they do that occurring naturally

PHYSICAL AND PSYCHOLOGICAL FACTORS IN SEBORRHOEIC ERUPTIONS

With the exception therefore of the comedo all the so-called seborrhoeic eruptions would seem to be due to the active growth, either in the *stratum corneum* or in the pilo-sebaceous follicles, of organisms which constitute the natural flora of the skin (the pityrosporon *Micrococcus cutis communis* the microbacillus of acne (*Corynebacterium acnes*)) or are very commonly present on it (*Staphylococcus pyogenes albus Staph aureus*)

The hormonal factor

We have now to consider the factors that favour the transformation of these organisms from inactive saprophytes into active parasities with pathogenetic effects Of these, from the evidence already adduced, it is clear that the hormonal factor is of primary importance. We have seen that not only do androgens

conception of biotropism Millan (1929) considered the acneiform eruptions caused by ingestion of bromides and iodides, for example, as being due to the stimulating action of these halogens on the growth of staphylococci in the follicles, and it is conceivable that androgens might have a like action in certain subjects. Goldsmith (1936), however cultured pustules of iodide acne and found them to be sterile.

(3) That, while admitting the roles of androgens and of individual predisposition, the development and severity of the inflammatory seborrhoeic eruptions depend upon other factors. In my opinion these factors are *diet, mode of life* and perhaps *emotional disturbances*

Diet and metabolism

Of these three alternatives, the third is the most acceptable and is supported by clinical experience, for it is unquestionable that the inflammatory lesions of acne, seborrhoeic dermatitis, sycosis, and, in some cases, furunculosis, can be markedly influenced both by suitable dietary and by a vigorous outdoor life, and that neither of these measures would decrease androgen formation. I have been interested in the influence of diet on seborrhoeic eruptions since, with Dr Semon, I studied the severe cases that occurred among the troops in the first World War (Barber and Semon, 1918), and I dealt with the question again in my first Lettsomian Lecture (Barber 1929). Later the work of Földes (1933), on fluid and mineral retention, afforded one explanation of the conclusion at which I had already arrived, and this was reviewed briefly by me (Barber 1939)

> The subject of retention and mobilization of water and minerals is extremely complex, but is of the highest importance in a large number of morbid conditions, as is being increasingly recognized at the present time We are concerned only with the influence of retention and mobilization of fluid on the growth of bacteria, and it would seem that a waterinesss both of the skin and of the mucous membrane of the upper respiratory tract, favours bacterial activity whereas dietetic and other measures designed to eliminate and prevent fluid retention inhibit it.
>
> Briefly it may be said that whereas proteins, and particularly nucleo-proteins, cause increased elimination of water excess of carbohydrates and fats predispose to its retention. The diuretic effect of a protein-rich diet is doubtless in part due to urea, and nucleo-proteins contain purine bases which are chemically related to the caffeine group of diuretics.
>
> The remarkable difference in the volume of urine excreted on a diet rich or poor in protein was shown by Folin—1 170 cubic centimetres as compared with 385 cubic centimetres. When large quantities of fluid are drunk, absorption is rapid, but little dilution of the blood occurs. The excess of fluid is mobilized in the tissue spaces (for example those of the liver muscles, and skin), and normally is later absorbed and excreted by the kidney It can be understood, however that on a dietary relatively high in carbohydrate and fat and low in protein, more or less permanent retention of fluid in the tissue spaces will occur particularly if the fluid intake be excessive. In the actual oedema of malnutrition there is, of course, lowered concentration of plasma proteins and particularly of albumen, so that the albumin-globulin ratio is altered these changes may be found in certain cases of eczema, chiefly of the extremities, associated with subcutaneous oedema.

Stokes and Sternberg (1939), in their analysis of the aetiological factors to be considered in the treatment of acne, emphasize the importance of water balance, and

and itching may be intense, so that from rubbing and scratching the eruption becomes lichenified, and a secondary neurodermatitis is engrafted on the primary eruption

In other patients the pilo-sebaceous *follicles are involved rather than the stratum corneum* and the various lesions of acne develop with or without rosacea. Indolent papules and pustules on the chin are particularly common. As might be expected the appearance of these eruptions is often accompanied by fall of hair on the scalp, chiefly as in the male on the vertex and temples, and by the growth of coarse hair on the upper lip the chin and elsewhere

If in these menopausal cases, the alteration in the androgen-oestrogen ratio be corrected by the administration of oestrogens, the eruptions may clear rapidly even with little or no local treatment.

Given therefore, the necessary priming of the epidermis and sebaceous glands by androgens, there are other factors that favour the pathogenic growth of at least some organisms in the skin particularly perhaps, of various strains of staphylococci. We may with Bloch (1931), regard the appearance of comedones at puberty and during adolescence as physiological and as comparable with the growth of pubic and axillary hair Individual differences in the degree of their formation may depend as Bloch said on the fact that the production of the sexual hormone is varied in strength in each individual or that the follicular apparatus of the skin (the receptor mechanism) is individually different in its sensibility to this hormone as, for example, the type of beard varies in different men From what is said above, it would seem to be clear that both the alternatives postulated by Bloch come into play namely the relative amount of circulating androgen and the degree of susceptibility to it of those follicles in which comedones may form. The same two factors are doubtless operative in determining the degree of hirsuties.

Bloch himself however distinguishes sharply between the comedones ('first phase') and the inflammatory lesions of acne ('second phase') He emphasizes that only the former can be brought into direct relation with endocrine processes in the sexual glands He does not attempt to explain the pathology of the latter phase beyond suggesting that it is an example of a normal physiological action of a ductless gland becoming pathological.

Multiple causes of inflammatory lesions

Apart from comedones, one might also regard some degree of simple dandruff as almost physiological in virile males and in females during the unstable periods of puberty and adolescence but the inflammatory lesions of acne and of seborrhoeic dermatitis present a distinct problem. To account for them at least three alternative possibilities may be considered

(1) That in certain susceptible subjects the androgenic hormone itself is capable of provoking inflammatory reactions in the skin and pilo-sebaceous follicles. This is theoretically improbable, but the production of papular and pustular acne of considerable severity in some eunuchoids and castrates, merely by administration of testosterone, might seem to support this view

(2) That in some persons androgens excite the active growth of organisms already present in the skin. This could be regarded as an example of Milian's

eruptions, such as severe seborrhoeic dermatitis, pustular acne, sycosis, and furunculosis (2) those with chronic or recurring streptococcal infection of the skin and mucous membranes (3) those with multiple manifestations of the so-called allergic state (the eczema-prurigo-asthma-rhinorrhoea-migraine syndrome), in whom, from infancy retention of fluid and its mobilization in various tissues is one characteristic.

In the seborrhoeic group of cases, however there is another possible factor to be considered, namely that termed by Campbell and Burgess sugar intolerance (Campbell and Burgess, 1927 Campbell, 1931)

In their joint paper these authors reported on 31 cases (2 of which were pregnant women) of dermatoses of various kinds, in which they found low sugar tolerance with or without delayed assimilation as determined by glucose tolerance tests. It is difficult to analyse these cases clinically 60 per cent of the patients were over 50 years of age, but few young persons were tested. In some the eruption was labelled dermatitis in others eczema The majority appeared to be instances of intolerance of the skin of exposed parts to banal or occupational irritants. In some the flexures were chiefly involved, and others were cases of chronic and hyperkeratotic eczema of the hands. Treatment with a sugar-free or low-carbohydrate diet was successful in the majority of patients, several of whom had proved to be refractory to other measures. Some relapsed when the diet was relaxed, but responded promptly to its resumption

Campbell (1931) later recorded the results of sugar tolerance tests in 132 cases of various skin diseases. In this series intolerance was found in a number of young persons—10 patients being under 20 years of age and 32 per cent under 30 In order to combine the indications of intolerance, as shown by a high initial rise, and of delayed assimilation (slow return to normal), Campbell estimated the average percentage of sugar in the blood for the 2 hours following the administration of 100 grammes of glucose, and he regarded delayed assimilation as of greater moment than intolerance alone. An average figure of over 120 milligrams per cent was considered by him to indicate intolerance of sugar

It must be remembered, however that the character of the sugar tolerance curve depends upon a person previous diet. If this has been poor in carbohydrate, the rise is high and the decline is slow If the previous intake has been high, the test ingestion produces only a slight and irregular alteration in the blood-sugar (Himsworth, 1940) Presumably in Campbell's cases the carbohydrate intake had not been low and therefore his figures are probably significant. Some were very high and the patients proved to be unsuspected diabetics

Among his cases were 15 of seborrhoeic dermatitis, of which 11 were considered to give abnormal curves. Out of 12 cases of resistant pustular acne in adolescents, 9 showed intolerance, and all these patients improved rapidly on a low-carbohydrate diet.

Campbell considered that an abnormal percentage of sugar in the blood lowered the resistance of the skin to potential external irritants, and pointed out that in such cases the skin may take up excess of sugar the concentration in it being almost as high as in the blood (Folin, Trimble, and Newman, 1927). He also quoted Usher and Rabinovitch (1927), who showed that the sweat may contain an abnormal amount of sugar in persons with intolerance, and he suggested this may favour the development of seborrhoeic dermatitis and other dermatoses involving the flexures.

These observations lead us directly to Urbach's recent conception of skin diabetes or independent cutaneous glycohistechia which is based on the estimation of sugar in the skin by microchemical examination of excised pieces (Urbach,

the unfavourable effect of those influences that favour cutaneous hydration, such as excess of carbohydrate and the premenstrual retention of water and salt.

Deficiency of the vitamin B complex (particularly of thiamine, and perhaps of nicotinic acid) also tends to produce fluid retention it must be remembered that the greater the intake of carbohydrate the greater the need for vitamin B, and that deficiency of the latter is better tolerated on a low carbohydrate diet.

From these considerations one may conclude that a diet which is likely to provoke fluid retention and mobilization in the tissues is one containing a large proportion of carbohydrate and to a less extent, of fat, insufficient protein and vitamin B, and including a large fluid intake. Even if the amount of protein be adequate, a relative excess of carbohydrate and fat may produce similar effects.

An anti-retentional dietary on the other hand, should contain a relatively large proportion of protein and nucleo-protein, with vegetables, fruit, and dairy products, but with the amount of carbohydrate, fat, and fluids determined by the mode of life and environment. The carbohydrate foods taken should consist chiefly of those containing vitamin B An example of such a diet, given by Földes, contained 112 *grammes of protein, 150 grammes of carbohydrate, 38 grammes of fat,* 0·27 grammes of purine nitrogen, and 1,200 cubic centimetres of liquid allowing 400 cubic centimetres for fruit and fruit juices

Two cases under my own care that illustrate the effects of anti-retentional treatment may be cited.

Case 3 —A young man with very severe, widespread, and eczematized seborrhoeic dermatitis was in the habit of drinking 5 pints of beer every evening and about 2 pints of other fluids during the day His intake of carbohydrate foods of high calorific value was excessive In spite of the large fluid intake in the evening, he never urinated during the night, and the specific gravity of the early morning urine was 1·035 After a fortnight's treatment with an anti-retentional dietary and restriction of fluid to 3 pints daily which produced copious diuresis, serous oozing had ceased completely and the eruption responded to simple topical applications.

The second case affords a remarkable instance of its efficacy

Case 4 —A boy aged 15 years was referred to me some years ago by one of my colleagues under whose care he had been for asthma, because he was subject to frequent colds, with each of which acute impetigo of his nasal vestibules and upper lip developed. Apart from his asthma, he had chronic catarrh and *functional albuminuria*. On questioning the mother I learnt that the boy ate large quantities of sugar sweets, cakes, jam, puddings and white bread He was put on an anti-retentional dietary and, much to the mother's astonishment, his catarrh and asthma ceased within a fortnight, and the albuminuria disappeared. He remained free from colds and asthma *until the following* Christmas, when he was allowed to relax his diet. The result was a prompt return of his catarrh and asthma, and a cold and impetigo developed. When the anti-retentional dietary was resumed, his symptoms disappeared, and he remained well until he again relaxed his diet at Christmas.

This case has been under observation for several years, and the mother has noticed that, apart from the disappearance of active symptoms, the boy's physical and mental activities have been greatly increased under the anti-retentional regime.

Földes has emphasized the decrease in the frequency and intensity of colds in patients under anti-retentional treatment, and I can fully confirm his contention.

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On the other hand, Földes (1933) associates certain forms of psychosis with retention either chiefly of minerals ('salinous constitution') or of water ('hirudine constitution'). In the former case the mental state is that of anxiety neurosis or of depressive psychosis, although the patient's affairs may not warrant apprehension; in lesser degree he may be merely irritable without cause or highly strung. In the latter case the picture is different; there are alternating periods of lack of emotional response with inability to concentrate and of exceptional mental activity with euphoria. Such alternation is observed in allergic subjects, and it is notorious that a state of euphoria often precedes the paroxysms of allergic symptoms, gout, and epilepsy. Dostoievsky, who was an epileptic, observed that his most inspired moments preceded his attacks.

Földes publishes details of cases of profound nervous and psychical disturbances in which the symptoms were completely relieved by anti-retentional treatment, and in pre-war days, when such treatment was possible, I have observed many others.

Care must be taken, therefore, before ascribing a person's physical symptoms wholly to his psychological state, since the latter may well depend upon a metabolic error, the correction of which may completely change his mental outlook.

SUMMARY

(1) The influence of androgens and of oestrogens upon the *stratum corneum* and the sebaceous glands is discussed. Evidence is adduced that androgens stimulate the process of keratinization in both the surface epithelium and the pilo-sebaceous follicles, and the activity of the sebaceous glands, whereas oestrogens exert a contrary effect.

(2) The hormonal control of the distribution and growth of coarse hair is considered and its distribution in normal males and females contrasted. In females the growth of pubic and axillary hair appears to be primarily dependent not upon ovarian function, but upon an androgenic hormone derived from the adrenal cortex. A similar growth of feminine configuration occurs in males in the absence of gonadal influence, and is also presumably due to adrenal androgen. Coarse hair on the face, trunk, and limbs results from stimulation of the hair follicles by androgen, which in normal males is derived chiefly or entirely from the gonads, and in females, when it occurs, from the adrenal cortex. The hair follicles on the vertex and temporo-frontal regions of the scalp are exceptional, in that growth of hair in them is stimulated by oestrogens and inhibited by androgens; hence the occurrence of baldness in varying degree in a high percentage of males, and in some females with ovarian insufficiency or virilism, and at the climacteric.

The progress of alopecia of male type is arrested during pregnancy from the beginning of the third month, and this is accompanied, as a rule, by diminished activity of the sebaceous glands, and by the disappearance of dandruff and of seborrhoeic eruptions, such as acne. These changes are attributed to the progressive rise in the oestrogen content of the blood that occurs from the end of the second month of pregnancy to term.

(3) It is emphasized that the ratio between circulating androgen and oestrogen and the degree of sensitivity of the different tissues to hormonal influence are

1945) The average sugar content of human skin is said to be 58 milligrams per 100 grammes Any figure over 68 milligrams is regarded as pathological. The average ratio between skin sugar and blood-sugar is 61 per cent. When the ratio is 70 per cent or more, the case is considered to be one of cutaneous glycohistechia. The usual clinical picture in such cases is a syndrome of furunculosis, hidradenitis suppurativa eczema, and pruritus. A low-carbohydrate dietary sometimes combined with insulin, causes a fall in the amount of sugar in the skin with marked improvement in the eruptions

In my own opinion these observations of Campbell and Burgess and of Urbach are of great importance, and since 1919 I have advocated the treatment of active seborrhoeic eruptions, as well as of certain other dermatoses, by restriction of concentrated carbohydrate foodstuffs. With Dr Erskine, for example, I have found the intake of sugar and other sweetstuffs to be almost incredibly high in some patients with sycosis barbae, and in one case the average daily intake of sugar alone was 80 lumps or teaspoonfuls!

It is only fair to point out however that Crawford and Swartz (1936) claimed that carbohydrate by mouth and by intravenous injection improved rather than aggravated acne, and that Kulchar (1936) found that most dermatoses are not associated with abnormal carbohydrate metabolism, as judged by fasting blood-sugar estimations and by glucose-tolerance tests.

Sutton (1941) regards acne vulgaris as a pustular lipoidosis and advises treatment by exclusion of nearly all fat from the diet, with thyroid medication to the limit of tolerance I discussed the influence of fats on sebaceous secretion in my first Lettsomian lecture (Barber 1929) since it would appear that the composition of sebum may be altered by ingested fats, this might explain the deleterious effect of chocolate, cheese, and pig-fat in some cases of acne. The therapeutic effects claimed by Sutton, however might be due rather to the action of thyroid on the metabolic rate and as a diuretic than to the low fat intake.

To sum up, a long clinical experience has taught me that the severer forms of the seborrhoeic eruptions—pustular acne, seborrhoeic dermatitis, and sycosis—can be favourably influenced by restriction of carbohydrates and fats, or alternatively by increasing the amount of muscular energy expended. To what extent the benefit depends upon the prevention of fluid retention and cutaneous hydration, or upon the direct reduction of circulating sugar or fat, it is difficult to say

Urinary acidity.—Two other points remain for consideration In the more cute and severe seborrhoeic infections there is usually a high urinary acidity d the amount of alkali required to render the urine alkaline may be astonishing. his was very apparent in the cases studied in the first World War In such cases e administration of sufficient alkali to restore the urinary pH value to normal ay be of striking benefit but this may be partly due to the resulting diuresis.

notional disturbances

Lastly the influence of emotional disturbances on resistant seborrhoeic erup- ns is sometimes undoubted and was particularly studied in the second World ar It may well be that the influence of such disturbances, for example the xiety state is dependent upon fluid retention the emotional stress acting on the pothalamo-pituitary mechanism and leading to increased secretion of the anti- iretic hormone.

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important factors in determining individual variations in signs and symptoms due to stimulation by the sex hormones

(4) The features of the cutaneous state, named by Darier *la kérose* are described and are attributed to stimulation of the epidermis, hair follicles, and sebaceous glands by androgens The presumptive and the direct experimental evidence for this view are discussed. The effects of administering testosterone to females eunuchs, and male castrates, and of oestrogens to virile males and to females with seborrhoea and seborrhoeic eruptions, are contrasted

(5) The role of the pityrosporon of Malassez, the acne bacillus, *Micrococcus cutis communis* and other strains of staphylococci, in the genesis of the so-called seborrhoeic eruptions is considered. The nature of comedones, and the conflicting views on the bacteriology of acne papulata, pustulosa, and indurata are discussed The experimental production of seborrhoea, comedones, and acne papules and pustules, in cryptorchids, eunuchoids, and adult male castrates, by the administration of testosterone, is reviewed.

(6) The influence of diet mode of life, and emotional disturbances upon the seborrhoeic eruptions is discussed

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intruders taking advantage of a suitable medium in which to proliferate or truly pathogenic agents concerned in the production of the lesions and in a failure of the skin to heal. Also if the bacteria are actively concerned in the production of pathological processes, it has yet to be defined whether they stand in a primary causal relationship to the lesions or whether they are secondary intruders. The traditional criteria which used to be employed in deciding that organisms stood in causal relationship to diseases were the postulates of Koch. Modified criteria which are more often utilized at the present time may be stated as follows

(1) Constant association of the organism with the disease.

(2) Reproduction of the disease by pure cultures of the organism.

(3) Immunological changes in the host associated with recovery from infection and directed specifically against the organism.

For the most part, bacteriological studies of the skin have been concerned solely with experiments to test the first and second criteria and in only a minority of instances have they been extended to the third criterion. Other investigations from which deductions concerning the role of the bacteria have been drawn include, however epidemiological studies with particular reference to evidence of contagion with reappearance of the same organism in the new cases of the disease, and response to treatment aimed at eradication of the bacteria by specific antibacterial agents. The latter studies have been carried out particularly since the introduction of sulphonamides and of antibiotic agents such as penicillin. Though useful in confirming the evidence obtained from direct investigations of the bacteria and of the host-parasite relationship, the latter furnish the more exact knowledge and are indispensable in any final conclusions.

It is proposed now to discuss some of the points arising from recent work on the bacteriology of the skin with particular reference to the pyodermas, including impetigo, furunculosis, and sycosis barbae, in the aetiology of which infection by bacteria appears most likely As the bacteria believed to be concerned in the aetiology of these conditions are also found in the lesions of eczema, seborrhoeic dermatitis, and of contact dermatitis after they have become secondarily contaminated, the discussion will centre around the bacteriology rather than the particular clinical manifestations.

THE ORGANISMS

Identification of pathogenic bacteria and of specific types of organisms

Though a very large number of bacterial species is encountered on either the normal or diseased skin, many are relatively uncommon, and some are known to be non-pathogenic. Among the latter may be listed certain strains of staphylococci, diphtheroids, and non-haemolytic or α-haemolytic streptococci (*Streptococcus viridans*). The coliform organisms, proteus and pyocyaneus, though pathogenic, are only occasionally met with and are associated particularly with deep lesions of the skin such as wounds or deep burns. They are, however relatively unim portant in diseases of the skin in comparison with the commonly encountered pyogenic staphylococci and haemolytic streptococci. Much has been learnt in

CHAPTER 7

BACTERIOLOGY

C H STUART HARRIS

THE PART PLAYED BY BACTERIA IN THE CAUSATION OF SKIN DISEASES AND THEIR INFLUENCE ON HEALING

IN the early years of the present century the great masters of dermatology visualized the aetiology of skin diseases in terms of the particular micro-organisms found associated with the lesions. They therefore classified many skin diseases according to their assumed bacterial causes, and this practice has remained until the present day in the descriptions of the staphylococcal, and streptococcal diseases and so on (Darier *et al* 1936) In view of the comparative infancy of the science of bacteriology at the time, dermatologists appeared some years ago to have been in the forefront of descriptive pathology and their bold example might have led to a general adoption of a classification of disease in terms of aetiological agents. However such a classification has never been adopted though greater justification existed for it in the case of the diseases of some other organs than for the skin. Instead it is the dermatologists who have tended to retreat from their advanced position and who seem to have become increasingly uneasy about the wisdom of their system. Rejection of the hypothesis that disease can ever be attributed to single micro-organismal causes has led to the doctrine of the multiplicity of causes (Stokes, 1940) so that one might imagine that the species of bacteria found in the lesion is less important than the biochemical properties of the particular skin which is involved Others appear to have plumbed the depths of despair in concluding that the particular bacteria which may be found in a lesion depend entirely on the skill and technique of the investigator who if sufficiently meticulous would find streptococci, fungi, and even viruses in practically any lesion or normal skin (Sulzberger 1940) It may perhaps be just to attribute this débâcle to the fault of the bacteriologist rather than to the dermatologist, but it is highly probable that the situation has arisen because of a lack of co-operation between both experts in the two different fields

The purpose of this chapter is to review some of the more recent knowledge in connexion with the bacteriology of normal and of diseased skin and to glimpse some of the possible lines along which further investigation would appear worth while. No attempt will be made to give an exhaustive account of diseases in terms of bacteriological agents while specific diseases such as tuberculosis, syphilis, and the manifestations of fungal infection will be omitted

The bacteria associated with lesions of the skin

Present doubt concerning the bacteria found in lesions of the skin does not arise from inability to confirm their presence. Rather it arises from an interpretation of their role and from attempts to define whether they are casual harmless

particular outbreak. Incrimination, then, of one particular type of streptococcus would point to the probable existence of a strain with particular power of spread. Though unproven, it may be that the essential difference between cases of impetigo occurring in families or institutions and those comprising entirely sporadic infections, is that the strain of organism involved in the former but not the latter has the power of epidemicity. Until more information is obtained concerning staphylococcal types nothing can be said regarding the possible existence of epidemic types in skin disease beyond the fact that there seems no reason why such should not exist as in the case of the other cocci.

Correlation of the presence of pathogenic bacteria with lesions of the skin

Exact knowledge of the bacterial flora of normal skin is a prerequisite to the interpretation of bacteria found in skin lesions. Unfortunately the fact that the development of tests for distinguishing pathogenic from non-pathogenic bacteria is of comparatively recent date, has meant the discarding of much earlier information concerning normal skin. Recently however the study of cross-infection of wounds (Miles *et al.*, 1940) and of the mechanism of air-borne infection (Hare and Mackenzie, 1946) has added considerably to knowledge which has been of value not only to the dermatologist, but to the surgeon and in particular the plastic surgeon. It will, therefore, be as well to detail the conclusions as to the relative incidence of occurrence of pathogenic bacteria and in particular the *Staphylococcus pyogenes* and *Streptococcus pyogenes* on normal skin. Gillespie, Devenish, and Cowan (1939) found pathogenic staphylococci on the skin of 19.5 per cent of normal individuals, but somewhat higher values (24 per cent) were recorded by Martin (1942). Miles, Williams, and Clayton-Cooper (1944) reviewed the findings of many workers and themselves found pathogenic staphylococci on the skin of the wrist of 10–20 per cent of normal adults. Williams (1946) has recently shown by examination of 11 different skin sites on the same individual that pathogenic staphylococci may be found on at least one site at any particular time in 70 per cent of normal individuals. Group A haemolytic streptococci are in contrast relatively infrequent on normal skin. Though Hare (1941) recorded a gross incidence of 6 per cent of haemolytic streptococci on the skin of 248 normal individuals, only one of the strains belonged to Group A. Colebrook, Maxted, and Morris Johns (1935) found 7 Group A strains among 18 strains of haemolytic streptococci recovered from the hands of a group of 181 factory workers, yet Colebrook *et al.* (1944a and b) express the view that on the whole Group A haemolytic streptococci are relatively rare inhabitants of the normal skin.

The source of both pathogenic staphylococci and streptococci is a matter of some importance. While it is probable that non-pathogenic staphylococci may live in the sweat glands, it is highly improbable that pathogenic staphylococci or Group A haemolytic streptococci can do so. All the evidence suggests strongly that they come from the individual's own nasopharynx by the expulsion of infected droplets (Duguid, 1946. Hare and Mackenzie, 1946). Thus skin carriage of these pathogenic organisms is probably of subordinate importance to carriage in the respiratory tract, and the relative frequency of staphylococci and streptococci in the upper respiratory tract of normal individuals is correlated with the relative frequency of the same organisms on the skin.

connexion with the latter organisms since the elaboration of laboratory tests whose results could be correlated with the particular strains of organisms concerned in disease and which could, therefore, be used as tests for pathogenicity. Tests for pathogenic staphylococci now accepted and in common use are the production of toxin (haemolysin), fermentation of mannitol, and particularly the production of coagulase (Cruickshank 1937, Cowan 1938). By these tests it is now clear that colourless or achromic variants of the *Staphylococcus aureus* are frequent and are no less pathogenic than strains which possess the power of forming yellow pigment. The term *Staphylococcus albus* has, therefore, become largely meaningless, as it may include both pathogenic and non pathogenic strains of staphylococci.

The pathogenicity of haemolytic streptococci is usually decided by classification serologically on the basis of Lancefield's precipitin test (1933). Of the various groups, Group A (*Streptococcus pyogenes*) includes the majority of strains encountered in human disease and the fact that the strains encountered in diseases of the skin also belong to Group A indicates their pathogenic power, potential or actual.

In addition to the development of critical tests for distinguishing pathogenic from non-pathogenic strains, methods have been elaborated for the identification of specific sub-types among both staphylococci and haemolytic streptococci. In the latter bacteria the method of slide-agglutination described by Griffith (1934) has been in use for a sufficient time for its value to be appreciated. Such type identification enables comparison between the organisms of one patient and those of his contacts or neighbouring patients, or between the organisms from different regions of the same patient, or between those recovered at different stages of the disease. An analogous method of type identification among pathogenic staphylococci is that introduced by Fisk (1942) and Wilson and Atkinson (1945) which utilizes the bacteriophage method employed so successfully in the case of typhoid bacilli (Craigie and Yen 1938). The method is too recent for much experience to have been recorded, but its potential usefulness is considerable.

Use, then, of these bacteriological tests has established first of all that the strains of haemolytic streptococci and staphylococci recovered from the lesions of skin diseases are in fact pathogenic. Some evidence in support of the existence of what is known as epidemic types as a factor in skin disease has also been obtained. This conception, which was experimentally studied by Topley and his co-workers (Greenwood *et al.* 1936), has been a fruitful one in explaining the occurrence of epidemics associated with a particular variant of a species of organism. The characteristic of epidemicity is undefined. It is probably not equivalent to virulence or lethal effect, but involves the unknown factor which endows an organism with power to spread from case to case, and thus to cause contagious disease. The existence of epidemic types amongst the pneumococcus group appears to be well established. In the case of haemolytic streptococcal infection of the throat there is evidence for the existence of epidemic strains responsible for school outbreaks (Griffith 1938). Such a strain (Type IV) was found by Mumford and Heppleston (1943) to be associated with an outbreak of various skin lesions in a group of children and adults. There is, unfortunately, no means of measuring this power of epidemicity in the case of strains of streptococci other than that of proving the identity of all the strains recovered from a

In summary *Staphylococcus pyogenes* was encountered in the lesions of 96 5 per cent and haemolytic streptococci in the lesions of 48 5 per cent of subjects. Serological study of a limited number of strains of the haemolytic streptococci indicated that 23 of 24 strains were of Group A. It was concluded that the gross incidence of both pathogenic staphylococci and streptococci exceeded the value which could be expected from a study of the bacterial flora of normal skin. It has been said that the mere presence of bacteria in skin lesions does not justify the view that the bacteria are concerned in a causal relationship to the lesions. Such a relationship would be much more likely if a constant correlation between the type of bacterial flora and the particular clinical manifestation of the skin lesions was demonstrated. Now impetigo is an excellent example of the fruitful results of correlated bacteriological and clinical studies, for much of the confusion which exists regarding the bacteria concerned in impetigo appears to have arisen from failure to distinguish the lesions of two clinically similar yet different conditions. Sabouraud (1900) insisted that impetigo contagiosa was always associated with a streptococcus, but Lewandowsky's work (1922) suggested that there were in fact two distinct clinical and bacteriological entities. One of these, christened the staphylococcal variety had bullous lesions, the other streptococcal had lesions consisting of stuck-on-crusts. Subsequent authors have largely confirmed Lewandowsky For instance, Epstein (1940a) confirmed the existence of an impetigo in which the lesions contained only staphylococci, and a glance at Table I shows a similar tendency in the work of Davies *et al* (1945) These authors found staphylococci only in 17 of 19 patients with bullous lesions (annular impetigo) but noted the invariable presence of haemolytic streptococci in addition to staphylococci in 18 cases in which lesions consisted of stuck-on-crusts (rupiform impetigo).

Apart from impetigo however Davies *et al.* (1945) found little evidence of a constant association of a particular bacterial flora with a particular type of lesion. Ecthyma lesions, it was found, always yielded haemolytic streptococci but the bulk of the other cases examined, which exhibited the lesions of impetiginized seborrhoea, yielded either staphylococci alone or staphylococci and haemolytic streptococci.

Pursuance of this theme of relationship between flora and particular clinical manifestations necessitates the mention of three other skin diseases by way of illustration Pemphigus neonatorum is a condition known to possess a considerable degree of contagion (Poole and Whittle, 1935 Elliott, Gillespie, and Holland 1941) Apparently its lesions always harbour the *Staphylococcus pyogenes* and as pointed out by Epstein (1940a), resemble clinically those encountered in the staphylococcal variety of impetigo Next, erysipelas may be cited as an example of constant correlation between a particular organism—in this case the haemolytic streptococcus—and a particular series of clinical manifestations. The condition of acne also deserves mention. Some authorities (Fleming, 1909) regard the acne bacillus as a highly significant organism in relation to the causation of the lesions, yet staphylococci appear to be found frequently as well. It may be that a more elaborate study needs to be undertaken in order to establish or refute the constant relationship of the acne bacillus with acne lesions and

Staphylococcus pyogenes is frequently found in the upper respiratory tract in normal individuals Miles Williams, and Clayton-Cooper (1944) recorded that 47·4 per cent of subjects (hospital out patients) yielded coagulase-positive, and therefore pathogenic, staphylococci on nasal swabbing and noted the correlation between skin and nasal carriage. Lower figures are recorded by others such as Gillespie Devenish and Cowan (1939) with 43·4 per cent and A N Smith (1941) with 32 per cent nasal staphylococcal carriers. But, as pointed out by Williams (1946), the average carrier rate fails to give a complete picture of the magnitude of the nasal reservoir of staphylococci since in a ten week period 80–90 per cent of people carry pathogenic staphylococci in their nose at some time. Williams also showed, by phage-typing the strains of staphylococci that the majority of the strains recovered from hand and nose of the same individual belong to the same type, thus indicating the interdependence of the two forms of carriage.

The *Streptococcus pyogenes* however though commonly present in the throat is less frequently found in the nose. Straker Hill and Lovell (1939) indicated that though 6–13 per cent of throat swabs of normal individuals contain *Group A* streptococci nasal swabs were infrequently positive. There is, however clear evidence that nasal carriers can contaminate their environment more thoroughly than throat carriers (*Hare, 1940 Hamburger et al 1945*) Furthermore, the examination of the skin of nasopharyngeal carriers of Group A streptococci by Hare (1941) indicated that carriers seriously infect their own persons and in particular the hair of the scalp and the skin of the face and hands. Nasal carriers contaminate their skin more persistently than throat carriers.

From all this, it is clear that the mere presence of pathogenic staphylococci or Group A streptococci on the skin does not necessarily indicate that the organisms are actively concerned in the production of lesions of that skin. The bacteriological findings in a group of common conditions of the skin believed to be of infective origin and exhibiting various clinical manifestations can now be considered. Davies *et al* (1945) described the results of skin cultivation before treatment in 200 subjects suffering from impetigo contagiosa ecthyma furunculosis, and impetiginized seborrhoea and seborrhoeic dermatitis Table I indicates their results in detail.

TABLE I. CULTIVATION OF BACTERIA FROM CUTANEOUS LESIONS

Clinical group	*Staphylococcus pyogenes* alone	Haemolytic streptococci alone	Both staphylococci and haemolytic streptococci	Neither staphylococci nor haemolytic streptococci	Totals
Annular impetigo –	17	0	2	0	19
Sigilliform impetigo[1]	0	0	18	0	18
Ecthyma – –	0	6	5	0	11
Furunculosis –	4	0	0	0	4
Impetiginized seborrhoea and seborrhoeic dermatitis	81	0	66	1	148
Total – –	102 (51%)	6 (3%)	91 (45 5%)	1 (0 5%)	200

[1] Sigilliform is word derived from the Latin sigillum, seal.

(*After Twiston Davies, Dixon, and Stuart-Harris*, 1945)

TABLE II. INCIDENCE OF STREPTOCOCCI IN IMPETIGINOUS LESIONS

Duration of disease (days)	No. of cultures made	*Streptococcus pyogenes*	
		No. positive	Percentage positive
1–7	82	18	22
8–14	64	15	23
15–21	45	16	35
22–28	16	8	50
29–35	10	7	70
36+	13	10	77

(*After Bigger and Hodgson*, 1943.)

The analogy to the increasing secondary infection of burns by streptococci, with the passage of time is obvious (Colebrook *et al.*, 1944a and b). However no clinical differentiation of the various cases of impetigo was recorded by Bigger and Hodgson and a rising percentage of cases with streptococci after the fourteenth day could have been due to an elimination of the more rapidly healing staphylococcal cases, so that the more resistant streptococcal cases remained in a relatively high proportion. No evidence confirming Bigger and Hodgson's view was obtained by Davies *et al.* (1945), but really early cases of the disease were not examined.

The same argument applies to all skin lesions in which haemolytic streptococci are encountered. The findings could well be explained on the basis that the streptococci found, for instance, in ecthyma are implanted secondarily in the same way in which burns become infected. Few will doubt that this is the explanation for the presence of haemolytic streptococci and probably also of pathogenic staphylococci in eczematous or seborrhoeic lesions, or even in the dermatitis invoked by sensitization to the sulphonamides.

The exact source of the pathogenic organisms found in the skin lesions cannot with certainty be ascertained. There is little doubt that haemolytic streptococci reach the skin from elsewhere in the majority of cases for the normal skin rarely harbours these organisms. Nevertheless the sequence may be air-borne infection by dust or by infected droplets from outside, to the throat of the patient and then endogenous contagion from throat or nose to skin. Thus Cruickshank (1941) recovered the same serological type of haemolytic streptococci from the throats of 5 patients with impetigo as from their lesions. There is evidence that in erysipelas (Spink and Keefer 1936) an infection of the upper respiratory tract precedes an attack of the disease, while de Waal (1941) has recorded that 10 of 37 cases of erysipelas carried the same type of haemolytic streptococcus in the throat as in the skin. The possibility of endogenous infection from the nose or throat clearly exists and may well be a factor not only in causation, but in preventing successful elimination of organisms from the skin or in evoking clinical relapse. However as so many possible sources of direct exogenous infection also exist, for instance from infected dressings or blankets, only examination of the serological types of strains encountered and comparison with strains found elsewhere in the patient

techniques such as that of Craddock (1942) who employed penicillin to inhibit the overgrowth of the acne bacillus by staphylococci could be usefully employed.

Significance and origin of the bacteria found in skin lesions

Two questions which can be considered together emerge from the simple results of the bacteriological examination of the lesions of skin diseases. The first of these is whether the bacteria are to be regarded as primary or as secondary invaders and the second is whether they are derived endogenously from the same patient or from exogenous sources outside the patient

The fact that almost any breach of continuity of the epidermis becomes the site of bacterial proliferation has made it difficult to differentiate lesions which are initiated by bacteria from those where contamination of a pre-existing defect has occurred Indeed in the sense of initiation of a disease it appears likely that staphylococci or streptococci are seldom primary causal agents, as, for instance, the tubercle bacillus is in relation to tuberculosis. Some crack abrasion of the skin or other defect probably always provides the primary lesion and lodgement of pathogenic bacteria on this area induces the tissue reaction which is described as disease Nevertheless, there is a fundamental difference between such conditions as impetigo pemphigus, or erysipelas which may be called primary infections and which may actually exhibit epidemic or contagious characters and those in which skin lesions of a type such as eczema or contact dermatitis become secondarily infected

There appears to be some requisite change in character of the skin which enables bacteria to become established upon it. Some lesions of the skin, for instance psoriasis, do not tend to become invaded by bacteria and Colebrook (1930) mentions the rapidity with which haemolytic streptococci placed upon normal skin are eliminated. The whole subject of self-disinfection of the skin by natural means has now been studied extensively and is dealt with by Burtenshaw in this volume (Chapter 8)

In the case of actual skin lesions, the evidence as to whether any particular organism was present from the earliest stage of the lesion or whether it has become superadded to the lesion is essential before argument concerning the primary or secondary role of the invader can be entertained The recovery of *Staphylococcus pyogenes* from the earliest lesions of bullous impetigo and from vesicles whose surface continuity has not been broken argues in favour of a primary role for the staphylococcus in the causation of the disease (Bigger and Hodgson, 1943 Davies *et al* 1945). Similar conclusions may be reached in the case of pemphigus neonatorum (Poole and Whittle, 1935) The evidence in favour of haemolytic streptococci as a primary invader in impetigo is, however much weaker It is true that Cruickshank (1941) recovered haemolytic streptococci from the lesions of 15 of 23 cases of impetigo admitted to hospital between the second and seventh days of disease, but Bigger and Hodgson (1943) have brought forward evidence strongly suggesting that these organisms are in fact secondary invaders in impetigo Table II from their work shows that the streptococcus was by no means invariably present in cases examined early in the disease, but the incidence increased as time went on

success could not be obtained when the skin of the recipient was unbroken, scarification being an essential preliminary. These experiments were carried out both on a normal individual and on the normal skin of cases of impetigo. Similar results with staphylococcal cultures were obtained by Epstein (1940a) using the unaffected skin of a subject with impetigo. The experimental data quoted by Sheehan and Fergusson do not enable an estimate to be made of the degree of success likely with skin of entirely normal individuals compared with that of the impetiginous subject. At any rate it seems clear that in the subject with impetigo a pure culture of a staphylococcus *may* produce fresh lesions upon skin which has been traumatized. The apparent inability of the haemolytic streptococcus to produce lesions resembling impetigo is significant and also the fact that lesions

TABLE III. TRANSMISSION OF ORGANISMS

	Impetigo fluid	*Staph. aureus*	*Staph. albus*	*Strept. haem.*	*Staph aureus and Strept. haem.*
Total inoculations	18	13	10	9	1
Lesions obtained Aborting vesicle	6	1	0	0	0
Crusting vesicle	8	4	0	0	1
Full impetigo	4	4	0	0	0
Other lesions	0	2	0	7	0
Negative	0	2	10	2	0

(*After Sheehan and Fergusson*, 1943.)

produced by mixed cultures of staphylococci and streptococci resembled those produced by staphylococci alone. Certainly these transmission experiments did not lend any support to the view that the haemolytic streptococcus had any primary aetiological role in impetigo, and this combined with all that has been said previously strongly urges the probability that the haemolytic streptococcus is essentially a secondary invader. Finally it must not be forgotten that the human subject is not the ideal experimental animal for transmission experiments. Within a few days of birth the baby acquires staphylococci on the skin or in the nose and his environment also includes haemolytic streptococci from an early age. The adult doubtless acquires varying degrees of resistance from prolonged contact with both organisms and such resistance may entirely vitiate transmission experiments with organisms in the form of artificial culture.

CHANGES INDUCED IN THE HOST BY INFECTION AND THE HOST-PARASITE RELATIONSHIP

The phenomena of infective disease as witnessed in nature are governed entirely by the reaction of the host-cells to the micro-organisms concerned. Without this host-parasite interaction there is no disease, as we know it, and therefore

will decide whether or not the infection of the skin lesion is merely a part of a more extensive invasion of the body surfaces as suggested by Martin (1942)

The source of pathogenic staphylococci in skin lesions also cannot yet be decided but as the nose and normal skin are so often contaminated with these organisms, *endogenous infection* is obviously possible. The *Staphylococcus pyogenes* is in fact a typical opportunist (T Smith, 1934) lurking in nose or skin crevice and awaiting any opportunity which arises for attack. The examination of normal skin in those with actual lesions elsewhere has shown scarcely higher rates of carriage than in normal individuals. Thus Davies *et al.* (1945) found pathogenic (coagulase positive) staphylococci on the skin of the chest in 35 of 111 cases (30 per cent) with various infective conditions. The skin of the face, however which was often affected by lesions yielded pathogenic staphylococci in 50 of 83 cases (60 per cent) Similar results were obtained by Martin (1942) The nasal carrier rate in the cases of Davies *et al* (1945) was not abnormally high (49 of 120 cases—40 per cent) Proof of endogenous infection awaits evidence regarding the actual types of staphylococci concerned and further work is clearly required It is, however inconceivable that small lesions of the skin do not readily become infected with staphylococci from the skin itself though the majority of lesions must heal without any abnormal tissue reaction to the organisms having occurred It is possible that there is a failure of disposal of staphylococci by the skin of individuals with seborrhoea or eczema, but much further work on the normal mechanism of disposal of bacteria and of abnormalities in this mechanism, in the victims of such diseases, is clearly needed The matter is not merely of academic interest, but involves the question of treatment to prevent re-infection of lesions from other parts of the body Finally exogenous infection even with staphylococci is also possible as shown by the occurrence of contagion in pemphigus neonatorum and possibly in impetigo The activity of epidemic types of staphylococci may be a possible explanation of such outbreaks.

EXPERIMENTAL TRANSMISSION OF SKIN DISEASE

The second consideration which permits the attribution of a specific causal role to bacteria associated with a disease is a transmission of the disease either directly with material from lesions or by the use of pure cultures of the bacteria. Attempts to reproduce the lesions of impetigo with cultures of staphylococci or of streptococci have been only occasionally successful.

Both organisms have, it is claimed reproduced the lesions after inoculation into the skin However the work of two groups of observers in the Army during the recent war has shown that successful transmission cannot regularly be obtained even with material from lesions themselves. Bigger and Hodgson (1943) thus failed to obtain transmission of impetigo either with skin material or with cultures of staphylococci or streptococci Sheehan and Fergusson (1943) were, however more fortunate. The details of their results are reproduced in *Table III*

Thus, both with fluid from the blisters or from under the crusts of impetigo lesions and with pure cultures of staphylococci obtained from such cases, successful reproduction of the lesions was obtained. The authors noted, however that

concerned. Such are the changes mentioned above. A second series of changes results in the case of certain bacterial infections from a specific alteration of the basic reactivity of the cell. These changes often referred to as allergic reactions, are due to sensitization to bacterial antigens. The studies of Rich (1944) and his associates on allergy in relation to tuberculosis have an application to other bacterial infections and particularly to infections due to bacteria which are repeatedly encountered during an individual's lifetime. The essential differences between such bacterial sensitization and the anaphylactic or atopic sensitization seen in serum reactions or pollen sensitivity are summarized by Forbus (1945). A fundamental difference is the fact that in the latter instance, the serum of the sensitized individual contains a substance which will passively transfer sensitivity to normal individuals (Prausnitz Kustner reaction). In bacterial sensitization the cells of the sensitized individual become altered, but passive transfer with serum to other subjects is unsuccessful. As pointed out by Caulfield (1936) contact dermatitis due to vegetable agents such as tulips are likewise differentiated from atopic dermatitis in the same way.

Many experiments have been made in order to demonstrate bacterial sensitization of the skin to organisms commonly met with. Epstein (1940b) described experiments with staphylococcal filtrates suggesting that *in impetigo the skin* affected by the lesions reacted allergically towards such filtrates. Boe (1945) discussed the work of other authors and described experiments on rabbits which indicated the possibility of inducing sensitization to filtrates of staphylococcal cultures. He deduced that such sensitization in the case of man was a factor in the habitual infection of some individuals with staphylococci leading to acne, furunculosis, carbuncles, or pyoederma. In his experiments passive transfer with serum was unsuccessful so that a change in the actual skin cells as a result of infection was probably occurring as indicated above. If allergy is important in human *skin infections, it would be most likely to manifest itself* in chronic or relapsing infections such as sycosis barbae or furunculosis. The localization and walling off which seems to be prominent in these conditions may be an effect of changed skin reaction towards bacterial products whereby the organisms are fixed by the local defence mechanism and prevented from indiscriminate spread. It is clear however that knowledge concerning this important subject of bacterial sensitization is at present scanty and that further study is needed. There is a need also for defining the chemical nature of the substances in bacteria which induce sensitization. Staphylococcal cultures even after filtration contain many chemical substances derived from the organisms, and also substances from the original culture fluid, and a more critical analysis is clearly needed. Meanwhile it is important to stress the factor of sensitization if only because much that is obscure therapeutically might be explained by a type of host reaction which only needed a smouldering infection to evoke a widespread cellular change.

Immunological changes

The defence mechanism of the body to invasion by bacteria, protozoa, and viruses alike involves specific chemical changes whereby antibodies of many kinds are poured forth to neutralize the foreign substances and to aid the phagocytes in their role of mechanical elimination of the invaders. Such chemical

in attempting to assess the role of bacteria in diseases of the skin, study of the phenomena in the host should give information of fundamental importance. Unfortunately however that which takes place initially in the reaction of the tissues to bacterial invasion is essentially the non-specific defensive change which goes by the name of inflammation and which is common to insults and injuries of all kinds The mere presence of inflammation as portrayed by vascular changes leading to reddening of the skin and to exudation is therefore of no differential value in distinguishing the reactions to bacteria as compared with those to inanimate physical or chemical agencies Some bacteria it is true, induce characteristic specific cellular changes in the host by which the disease associated with them can be recognized as, for instance the miliary tubercle in tuberculosis. Recognition of any specific histological changes of this sort would enable the deduction that the bacteria were acting as true pathogenic agents. In the absence of cellular changes, specific chemical changes observed in the host as a result of the development of immunity or resistance to bacterial antigens likewise assist in defining the role of the bacteria as one of active pathogenicity Finally, the bacteria in the skin lesions may fail to exact any characteristic cellular or immunological changes, but a delay in the process of healing occurs from the elaboration of noxious substances.

Cellular reactions

Both the staphylococci and the streptococci are often termed the pyogenic bacteria because their presence in the tissues is associated with an outpouring of leucocytes and the process of suppuration. Such a process is probably to be regarded as the basic pattern of the inflammatory response called forth by the various toxins and diffusible products of the bacteria or by chemical substances released from the cells dying from the effects of the bacteria. It is the essentially purulent nature of the exudate in conditions such as furunculosis and sycosis barbae and even the existence of leucocytes in the blister fluid of impetigo which has led to belief in the harmful effect of the bacteria also present. Active phagocytosis of cocci by the leucocytes present in the exudate can also be observed and is evidence of the defence mechanism in action. However differences exist in the inflammatory response associated with haemolytic streptococci as compared with staphylococci. The laudable pus associated with the latter must be contrasted with the more fluid exudate associated with streptococci. A greater degree of tissue destruction resulting in actual ulceration may also be seen in streptococcal diseases. There is little doubt that a tissue reaction to a mixture of streptococci and staphylococci would theoretically be expected to be different from that to staphylococci alone and thus a basis clearly exists for the different lesions observed in streptococcal compared with staphylococcal impetigo

Recent pathological studies have, however been more concerned with interpretation of the processes involved in infection rather than in adding to knowledge of morphological changes. In a thoughtful paper by Forbus (1945) a description and discussion of the reactions of tissues following infection is worthy of mention in connexion with the present subject. According to this author the changes seen at the site of entry of an infectious agent are initially the result of changed environment of the cells due to growth in their fluid medium of the bacteria

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Immunological changes

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changes are intensely specific to the invaders concerned, are developed with a variable degree of success against various organisms and are elaborated more readily by some hosts than by others. No better illustration of specificity can be given than that which is seen in the artificial immunization of animals to pneumococci The type-specific polysaccharide of the pneumococcus may immunize mice against the particular type of pneumococcus from which it was derived, but not against other types (Zozaya and Clark 1933) The same result appears to be obtained in man (MacLeod *et al* 1945) Similar results are obtained in virus diseases as, for instance, in the specific homologous immunity induced by influenza viruses A and B That different bacterial antigens vary in their immunizing powers is known so that for instance, Type I pneumococci more readily immunize animals, and probably humans as well than do Type III pneumococci (MacLeod, 1939) The variability in host response to the same antigen is, moreover abundantly proved by the known variation in the titre of antibodies elaborated in response to the same amount of inoculum introduced into different individuals. In addition to these three characteristics of the immune response, many others exist such as the fact that localized tissue invasions, for example influenza or the common cold produce a less durable or long-lasting immunity than do general systemic infections such as measles or enteric fever

The characters of the immune response to staphylococci and streptococci have been studied chiefly in relation to internal diseases and relatively little is known concerning the changes which occur in localized infections of the skin. The relapsing character of infections due to the staphylococci and streptococci does, however suggest that the body finds it difficult to establish an effective local immunity to these species. Perhaps this is due as much to the multiplicity of types concerned as to the superficial nature of the infection itself Studies of the serological changes in the blood which accompany infection certainly indicate abundant reaction to products of the bacteria Though the staphylococci elaborate many substances including coagulase and toxins such as haemolysin and leucocidin (Wilson and Miles, 1946) it is the antibody directed against the haemolysin which has been studied most Normal subjects possess a certain quantity of antihaemolysin in their blood and following upon internal infection with staphylococci the titre of antibody is raised considerably In superficial infections of the skin such as sycosis or furunculosis though some authors (Connor and McKie, 1933) found raised antihaemolysin titres the general opinion is that the titres are not raised as much as in internal disease and that they may be normal (Dolman 1933) Following inoculation with staphylococcus toxin or whole bacteria the antihaemolysin titre is greatly increased but it is important to realize that such antibody formation is not necessarily correlated with immunity to infection either in rabbits (Downie, 1937) or in man (Whitby 1936). Antileucocidin formation on the other hand which has been studied by Valentine and Butler (1939) may be correlated with recovery from deep-seated infection with staphylococci It does not appear to have been studied in more superficial infections

The study of staphylococcal antibodies has thus failed to throw any clear light upon the role of the staphylococci in connexion with skin diseases.

The haemolytic streptococci elaborate substances with haemolytic, toxic, leucocidic, and fibrinolytic properties (Wilson and Miles, 1946) and serum from subjects convalescent from streptococcal infections contains antibodies inhibitory to these substances. Again, the best studied antibody is that antagonistic to the haemolysin (streptolysin). Antistreptolysin has been studied chiefly in connexion with respiratory tract infections such as scarlet fever and tonsillitis or in relation to rheumatic fever or nephritis (Todd, 1932 Lyttle *et al.*, 1938 Mote and Jones, 1941). Good use has been made of the antibody in differentiating infection of the throat from simple carriage of the organism. (Commission on Acute Respiratory Diseases, 1945)

Antifibrinolysin is another antibody which has been much studied in connexion with enteral and respiratory tract disease (Tillett and Garner 1933 Tillett, Edwards, and Garner 1934 Hadfield, Magee, and Perry 1934 Stuart Harris 1935 Mote and Jones, 1941).

In erysipelas, Spink and Keefer (1936) have demonstrated that the antistreptolysin titre of the serum is elevated during and after the acute stage of the disease and that antifibrinolysin also appears in the blood as the disease progresses. They also found an increase in bactericidal power of the blood to haemolytic streptococci and concluded that all these changes indicated a response on the part of the host to streptococcal infection. A detailed study of both these antibodies in relation to other skin diseases would seem well worth while. In the meantime, it is important to stress that, as in the case of the staphylococcus, mere possession of good antibody titre is not equivalent to immunity at any rate towards localized infections. Nevertheless, if an effective immunizing antigen was developed against such bacteria immunological studies would furnish a useful tool in following the immunity process and in assay of antigenic potency

Reference must finally be made to the recent revival of an old conception of an immunological phenomenon. This is the conception of auto-immunization or the development by the body of antibodies to its own tissues or organs. Normally homologous organ extracts are not antigenic in the same species and injection of such extracts parenterally is not followed by antibody formation. Under certain circumstances, including infection, homologous protein does, however become antigenic. Gear (1946) has pointed out that liver from a monkey infected with yellow-fever virus is antigenic in other monkeys, whereas liver from a normal animal is not, and has considered the possible operation of a similar mechanism of autosensitization in blackwater fever Schwentker and Rivers (1934) found that brain from a rabbit injected with vaccinia virus was antigenic and induced specific antibody formation against brain substance upon injection. Cavelti and Cavelti (1945) have shown that kidney extracts admixed with haemolytic streptococci are thereby rendered antigenic and claim to have revealed the mechanism which results in the production of nephritis. Cavelti (1945) has extended these observations to rheumatic fever Burky (1934) showed that heterologous lens extracts were rendered powerfully antigenic by admixture with staphylococcus toxin and his findings were confirmed by Swift and Schultz (1936). These authors found, however that homologous lens material was only slightly antigenic by comparison with heterologous lens even after addition of staphylococcus toxin. Hecht, Sulzberger

and Weil (1943) have extended this work by demonstrating the formation of antibodies in rabbits immunized with homologous skin extracts and staphylococcal toxin. They claim that a synergistic antigenic complex is thus formed and that the process of auto-immunization could, in the human, result in the production of an exaggeration of existing skin lesions. Therapeutic tests based on the hypothesis have been made by Hopkins and Burky (1944).

Nevertheless, most of this work has been concerned in demonstrating the existence of antibodies in the blood after the various experimental procedures. That such antibodies may have an injurious action is obvious and the experiments of Cavelti and Cavelti (1945) certainly support the thesis. Much more will have to be done, however, before the role of auto-immunization in skin disease will be known. The theory is certainly promising and test of it should be given a place in future investigations.

Response to treatment

Some of the interest now revived in the role of bacteria in relation to disease of the skin probably arises from the introduction of potent chemotherapeutic and antibiotic agents with specific anti bacterial action. If a condition responds to treatment with such agents, it is possible that bacteria were originally the causative agents of the lesions. For instance, the rapid response of erysipelas to sulphonamides or to penicillin is in agreement with the accepted view that the condition is a true infection invoked by the *Streptococcus pyogenes*. However, the converse finding of a failure of response to therapy does not greatly assist in determining the role of the organisms. The attempt by Davies *et al.* (1945) to assay critically the value of penicillin in the treatment of bacterial skin infections resulted in a general failure to confirm the enthusiastic reports of others (Roxburgh, Christie, and Roxburgh, 1944; Taylor and Hughes, 1944; Hellier and Hodgson, 1945). The results indicated that conditions with a natural tendency to heal and of a self limiting character, such as staphylococcal impetigo, did respond dramatically to penicillin. Other conditions more resistant to healing such as streptococcal impetigo did not respond dramatically to penicillin any more than they did to other forms of treatment. A full discussion of possible reasons for this failure of local penicillin therapy is given by these authors and will not be repeated here. The fact, however, that neither staphylococci nor streptococci were actually eliminated from the lesions treated with penicillin means that sterilization of the lesions was not in fact obtained and no argument relating to the role of the organisms in relation to the disease is therefore possible. On the other hand, the contrast between the ready response to treatment by penicillin exhibited by staphylococcal impetigo compared with the slow healing of the lesions of the streptococcal variety recalls the phenomenon described by MacLeod and Stone (1945). MacLeod described the essential difference between the actions of sulphonamides and penicillin in the treatment of experimental pneumococcal infections in mice and attributed these to the fact that the former were merely bacteriostatic and depended for success upon the general immunity mechanism of the host, whereas penicillin, which is bactericidal, was less dependent on host factors for its action. However, though Type I and Type III pneumococci are equally sensitive to penicillin *in vitro*, infection of mice with the latter organism requires much more

prolonged therapy with penicillin before cure is attained. This, MacLeod suggests, may indicate that part of the therapeutic action of penicillin observed *in vivo* is dependent on the participation of some component of the animal body. The fact that immunity is developed in mice more readily to Type I than to Type III pneumococci is important in this connexion. It is clear therefore, that observations connected with a failure of response to therapy may not indicate that the bacteria are unrelated to the disease but that the host-parasite relationship is a complex one.

There is every reason to believe that this is indeed so in the case both of the staphylococcus and the haemolytic streptococcus.

The Host factor

Study of the host-parasite relationship in most infections has unfortunately been limited in the past far too much to the parasite and the reaction of the host has been sadly neglected. And yet, as already indicated, it is changes in the host which constitute the disease as manifested by clinical phenomena. At times some of the important factors which may govern the reaction of the host have been glimpsed, as, for instance, in attempts to define constitution in relation to dermatitis (Davies and Barker 1944). It is clear that constitution is of particular importance in conditions such as seborrhoea, but its possible relationship to others in which infection plays a larger part is quite unknown. Apart altogether from constitution other host factors are clearly of importance, however in relation to infection. The tendency of diabetics to develop serious infection as a result of trivial injury may be cited as an example. It is possible that this tendency may be merely an expression of the general susceptibility of diabetics to infections of many different kinds. On the other hand, there is evidence of a peculiarly intimate relation between carbohydrate metabolism and the skin, and diabetes is not the only condition in which the sugar content of the skin itself is abnormal (Urbach and Lentz, 1945)

The incidence of acne exhibits an age distribution which suggests the fundamental importance of the endocrines and in particular the changes accompanying adolescence, in this disease. Yet detailed study as for instance that of Cohen (1945), indicates that acne is still common in the late twenties or thirties and that the disease is by no means as confined to narrow age groups as has previously been believed. Clearly the time is ripe for the assembly of information now lacking on this vital subject of the constitution and metabolism of the human subject in relation to skin disease as a whole. The bearing of this knowledge upon the limited field of infections of the skin can then be appreciated.

THE INFLUENCE OF BACTERIA UPON HEALING

However much doubt remains concerning the aetiological role of bacteria in skin disease, there is little justification for doubting that infection delays healing. The studies of wound infection in World War I emphasized the importance of bacterial infection in delaying the closure of wounds and stressed the haemolytic streptococcus as the most important organism in this connexion. World War II

has not been attended by such grave problems of wound healing as was the former and this is attributable both to improvement of surgical technique and to the adoption of measures to prevent cross-infection and also to the use of sulphonamides and penicillin (Mitchell 1947) The plastic surgeon has long regarded bacterial infection as an enemy of his art and inimical both to survival of the graft and to ultimate epithelialization The studies of Colebrook and Francis (1941) indicated the fruitful results of controlling streptococcal infection of grafted areas with sulphonamide, and Francis (1942) indicated the trouble likely to arise when sulphonamide resistant streptococci were introduced into the wards. Colebrook and his co-workers (1944a and b) have attributed a leading role in the prevention of healing in burns in the first week to infection. They thought that the streptococci were of greater importance than the staphylococci in the causation of sepsis and the prevention of healing. Their whole technique of the management of burns and scalds was designed rightly or wrongly towards the prevention of the superadded streptococcal infection which seemed otherwise to be an inevitable event. Bodenham (1945) also considered that the haemolytic streptococcus could stop the growth of epithelium or even cause regression of the healing edge of burns or surface wounds and that the staphylococcus often had little or no retarding action on epithelialization

There is little doubt that these observations bear on the problem of streptococcal infection of skin lesions other than those of burns. The haemolytic streptococcus thus has a most important part to play in the prevention of healing of lesions of the skin of all types. Yet there is no knowledge of the method by which such an effect is produced The streptococci produce numerous substances, some of which have already been mentioned—haemolysins, fibrinolysins, leucocidins, and so on They are associated with a necrotizing process of the tissues. They secrete a substance (hyaluronidase) with an action upon the ground substance of connective tissue (McClean 1941) thus rendering the skin more permeable (Duran-Reynals, 1933) In view of the importance of the underlying connective tissue on the formation of the epidermis (Converse and Robb-Smith 1944) such substances may have an inimical action on healing of the skin. Knowledge is still far too scanty however to permit definite conclusions to be drawn concerning the mechanism of the antagonistic action of the haemolytic streptococcus to healing of the skin Nor is it clear whether the staphylococcus is important in the same way or not. It is known that the staphylococcus secretes substances antagonistic to cells and also the dermal spreading factor (hyaluronidase) alluded to above (Duran Reynals, 1933) Yet, in the experience of Colebrook *et al* (1944a and b), staphylococci caused relatively little sepsis and did not inhibit the rate of healing of burns to the same extent as haemolytic streptococci nor did they interfere with the success of grafting operations

Perhaps the most convincing evidence of the significance of cocci in the prevention of healing of surface lesions has been marshalled by Miles (1944) In a study of the small wounds and lacerations of the hand encountered in industry Miles defined the three grades of clean silent infection and septic and infected wounds. The time taken for wounds to heal in relation to these grades of infection are quoted in detail in Table IV The category of silent infection including wounds

which showed no clinical evidence of infection yet in which bacteria were found on examination, is of particular interest.

TABLE IV RELATION OF HEALING-TIME TO INFECTION OF HAND WOUNDS WITH *STREP. PYOGENES* AND *STAPH. AUREUS*

Type of Wound	Number	Healing-time (days)
Small industrial		
Clean	43	6·0±4·1
Silent infection	24	7·4±2·6
Septic and infected	15	16·7±7·0
Minor laceration		
Clean	80	15·6±4·1
Silent infection	59	18·2±4·6
Septic and infected	30	25·4±10·6

Bacteria present without clinical evidence of infection.

(*After Miles*, 1944.)

If these results with wounds are applicable at all to lesions of the skin, then bacteria truly exert a potent influence upon the rate of healing.

Finally the subject of healing cannot be left without a reference to the important coliform, proteus, and pyocyaneus bacteria. The pyogenic properties of these organisms render them important antagonists of healing of the deeper lesions of the skin, and their resistance to anti-bacterial agents effective against the streptococci and staphylococci increases their importance.

CONCLUSIONS

In conclusion and at the risk of adding yet another theory to a subject over burdened with theories and still in need of fundamental facts, let us attempt some sort of hypothesis of the possible *modus operandi* of the staphylococcus and streptococcus in relation to skin disease. The pyogenic staphylococcus is an organism frequently present on respiratory tract mucosa and skin alike, with existing or potential powers of pathogenicity yet for the most part content to live peacefully along with its human host. The relationship between organism and skin is formed at an early age of the host and is maintained throughout life. Though opportunities must occur every day for the disturbance of this equilibrium and for the translation of saprophytism into parasitism, yet the change must be determined by relatively infrequent circumstances. We do not yet know what determines these circumstances. Contrast this picture with that of the haemolytic streptococcus, a common commensal of the respiratory tract from which it finds its way to the skin, yet upon which it fails to thrive. Perhaps this ability of the normal skin to dispose of the streptococcus accounts for the fact that when the latter does enter into relationship with the skin, it is probably nearly always acting as a pathogen destroying, invading, inhibiting healing and generally aiding and abetting influences adverse to the health of the skin. Though the body is thus in frequent contact with the haemolytic streptococcus, the partnership is never so

has not been attended by such grave problems of wound healing as was the former and this is attributable both to improvement of surgical technique and to the adoption of measures to prevent cross-infection and also to the use of sulphonamides and penicillin (Mitchell 1947) The plastic surgeon has long regarded bacterial infection as an enemy of his art and inimical both to survival of the graft and to ultimate epithelialization The studies of Colebrook and Francis (1941) indicated the fruitful results of controlling streptococcal infection of grafted areas with sulphonamide, and Francis (1942) indicated the trouble likely to arise when sulphonamide-resistant streptococci were introduced into the wards. Colebrook and his co-workers (1944a and b) have attributed a leading role in the prevention of healing in burns in the first week to infection. They thought that the streptococci were of greater importance than the staphylococci in the causation of sepsis and the prevention of healing. Their whole technique of the management of burns and scalds was designed rightly or wrongly towards the prevention of the super added streptococcal infection which seemed otherwise to be an inevitable event. Bodenham (1945) also considered that the haemolytic streptococcus could stop the growth of epithelium or even cause regression of the healing edge of burns or surface wounds and that the staphylococcus often had little or no retarding action on epithelialization.

There is little doubt that these observations bear on the problem of streptococcal infection of skin lesions other than those of burns The haemolytic streptococcus thus has a most important part to play in the prevention of healing of lesions of the skin of all types. Yet there is no knowledge of the method by which such an effect is produced The streptococci produce numerous substances, some of which have already been mentioned—haemolysins, fibrinolysins, leucocidins, and so on They are associated with a necrotizing process of the tissues. They secrete a substance (hyaluronidase) with an action upon the ground substance of connective tissue (McClean 1941) thus rendering the skin more permeable (Duran-Reynals, 1933) In view of the importance of the underlying connective tissue on the formation of the epidermis (Converse and Robb-Smith 1944) such substances may have an inimical action on healing of the skin Knowledge is still far too scanty however to permit definite conclusions to be drawn concerning the mechanism of the antagonistic action of the haemolytic streptococcus to healing of the skin Nor is it clear whether the staphylococcus is important in the same way or not. It is known that the staphylococcus secretes substances antagonistic to cells and also the dermal spreading factor (hyaluronidase) alluded to above (Duran-Reynals, 1933) Yet, in the experience of Colebrook *et al* (1944a and b), staphylococci caused relatively little sepsis and did not inhibit the rate of healing of burns to the same extent as haemolytic streptococci nor did they interfere with the success of grafting operations.

Perhaps the most convincing evidence of the significance of cocci in the prevention of healing of surface lesions has been marshalled by Miles (1944) In a study of the small wounds and lacerations of the hand encountered in industry Miles defined the three grades of clean silent infection and septic and infected wounds. The time taken for wounds to heal in relation to these grades of infection are quoted in detail in *Table IV* The category of silent infection including wounds

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amicable as in the case of the staphylococcus and the body struggles with the streptococcus from birth onwards, never achieving indifference or mastery and often being maimed in the process.

The *multiplicity* of types of both organisms may be a factor in the induction of disease when that species to which the body has become adjusted becomes replaced by another more foreign variety Perhaps this is why in early life, the forms of disease associated with either organism partake of more contagious properties compared with those seen in the adult. Long acquaintance with the organism has then induced a degree of resistance or immunity whereby the would-be invader is *held locally* and prevented from too great an inquisitiveness. In such a close relationship as must exist between host and staphylococcus it is easy to see how abnormal responses productive of a vicious circle can arise. An unusually close linkage of body and organismal protein perhaps deceives the body into a failure to recognize its own tissue constituents In this way it may treat the combination as foreign elaborate antibodies to it and thus lead to a destruction of its own cells. Thus by ordinary bacterial sensitization and auto-immunization pathological processes may readily be instigated and the normal commensalism of the host and bacterium become converted into disease. The picture so drawn is that of a delicately balanced relationship between bacterium and human host in which the manifestations of disease appear to be the consequence of disturbed relations. We have travelled far from the usual interpretation of disease in terms of aetiological agents with which this chapter began and yet the link between bacterium and disease has emerged as even stronger than that apparent in so many infections where the host and its parasite undergo brief encounters perhaps accidental in nature and only occurring once in the lifetime experience of the host

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harmless. He discusses briefly the suggested production in the skin of specific immunity to certain diseases, for example, the warding off of tertiary lesions of syphilis in the central nervous system by antecedent secondary lesions in the skin. Kwiatkowski describes histological work, demonstrating in men and rabbits that substances such as congo red, Indian ink, and iron oxide injected intravenously are taken up by the histiocytes of the epidermis and by endothelial cells of the skin capillaries. This activity of the reticulo-endothelial system is much greater in the epidermis than in the corium, and is particularly striking in the area of a histamine weal.

Studies in acquired immunity

Many attempts have been made to determine whether the skin can develop an active immunity either specific or non-specific, independent of humoral immunity shared with the other tissues of the body. Meserowitsch (1888) amongst others, noticed that rabbits, after recovering from experimental erysipelas, were resistant to subsequent inoculations of the causative streptococcus during a period of 2 months. Gromakowsky (1895) supplemented this observation by showing that animals, which had become resistant to intracutaneous inoculation of streptococci, might still be infected intraperitoneally.

In a series of experiments Cobbett and Melsome (1895) proved that in rabbits an area of skin recovered from erysipelas cannot be re-infected during the next few weeks with the specific streptococcus, and that other areas of the skin are sometimes, but not always, protected against infection with the same streptococcus. These workers seem to have thought that the general skin immunity was of humoral type.

Similar work on rabbits by Gay and Rhodes (1922) demonstrated that not only the area of skin healed of erysipelas, but all other areas were immune to infection with the causative streptococcus for about 3 months. An attack of erysipelas was essential to the production of this skin immunity. Intracutaneous injections of killed streptococci were ineffective. Cutaneous immunity to the streptococcus was not associated with immunity to intravenous inoculation. This fact strongly supports these authors' view that there was built up a local skin immunity independent of any general tissue immunity.

Rivers (1925) found that there was a progressive increase of resistance to successive intracutaneous injections of erysipelogenic streptococci. After several such injections the animal's serum was tested for streptococcal antibodies by simultaneously injecting some of the serum and erysipelogenic cocci into the skin of a normal rabbit. A control was provided by injecting another skin area of this rabbit with erysipelogenic cocci and the same dose of a normal serum. The serum from the rabbit inoculated with streptococci gave far more efficient protection than did that of the normal rabbit, and Rivers concluded that it contained specific antibodies.

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CHAPTER 8

THE AUTOGENOUS DISINFECTION OF THE SKIN

J M L. BURTENSHAW

HISTORICAL INTRODUCTION

THE ancients thought of the skin as a membrane enveloping the body and protecting it from the slings and arrows of outrageous fortune Hippocrates has little to say about it, whilst Galen (A D 250) remarks The skin is a fibrous substance covering the entire surface of the body its purpose is to provide adornment, to act as an envelope, and to ward off harmful influences.

Sabouraud (1899) approaching the problem of skin function after the birth of bacteriology explains the process whereby the skin rids itself of bacteria in the the following way *La vie même de l'épiderme sa vie normale amène incessamment ses couches profondes à la surface ou elles s exfolient Il se produit donc une perpétuelle exfoliation des couches mortifiées et si elles sont microbiennes, une perpétuelle éviction des microbes qui vivent sur elles* In other words, bacteria in the skin are unable to invade the body except by proliferation into the dermis, and this is continually counteracted by the deeper layers of the epidermis approaching the surface and being shed

This view is endorsed by Metchnikoff (1901) who naturally emphasizes the engulfing activities of the phagocytes, not only in the dermis, but also in the epidermal rete mucosum and stratum granulosum. Koch (1908), Zangemeister (1910) and Grütz (1911) concur in the opinion that haemolytic streptococci and other pathogens are but rarely recovered from the skin except from that of persons constantly exposed to them such as midwives or patients with infected open lesions.

Later work may conveniently be discussed under two headings (1) disinfection in the skin, and (2) disinfection on the skin surface.

DISINFECTION IN THE DEPTHS OF THE SKIN

The well-known processes of inflammation and of humoral immunity operate defensively in the skin as in every other tissue. There is, therefore, no need to discuss these, beyond alluding to a review of the subject of self-disinfection of the skin by Mallinschrodt Haupt (1932) and to a paper by Kwiatkowski (1935), who has made ingenious experiments revealing the part played by the reticulo-endothelial system in removing noxious substances from the skin

Mallinschrodt Haupt says that Jena discovered amongst the skin proteins an albuminous fraction which destroyed many toxins and formed innocuous compounds with phosphorus and the heavy metals, and that Jesionek believed that the connective tissues of the skin can combine with tubercle bacilli making them

harmless. He discusses briefly the suggested production in the skin of specific immunity to certain diseases, for example, the warding off of tertiary lesions of syphilis in the central nervous system by antecedent secondary lesions in the skin. Kwiatkowski describes histological work, demonstrating in men and rabbits that substances such as congo red, Indian ink, and iron oxide injected intravenously are taken up by the histiocytes of the epidermis and by endothelial cells of the skin capillaries. This activity of the reticulo-endothelial system is much greater in the epidermis than in the corium, and is particularly striking in the area of a histamine weal.

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path of lymph drainage from the skin area first infected. Other neighbouring areas were not protected against streptococci injected into them. The whole skin, after many injections of organisms into one area, acquired some anti-streptococcal immunity but this generalized skin immunity was accompanied by the development of humoral immunity evidenced by the appearance of antibodies in the blood

These observations, except those of Gay and Rhodes, show that localized immunity can be conferred by previous infection of a skin area with streptococci, but that immunity over the whole skin is only acquired concurrently with generalized humoral immunity

The mechanism of resistance

What is the mechanism of this local increase of resistance to re-infection of the skin?

Cobbett and Melsome (1898) pointed out that a local inflammation of a rabbit's skin induced by injecting mustard oil effectively protected the injected area against subsequent inoculation with erysipelogenic cocci This protection was strictly local and these authors believed that it consisted in the greater speed with which the processes of inflammation such as the dilatation of vessels and the bringing up of phagocytic cells and antibodies, followed a second stimulus as the result of the practice acquired from the first.

Besredka and his colleagues (1923 1924) claimed that local immunization of the skin of rabbits could be effected by intracutaneous inoculation or poulticing of a skin area with bacterial filtrates that is, the broth filtered off from growths of streptococci or staphylococci They thought that these filtrates acquired properties toxic to the organisms because growth no longer occurred in the filtrates on re-inoculation

According to Mallory and Marble (1925) filtrates from cultures of streptococci and staphylococci injected into the skin of rabbits some hours before infection of the area with streptococci conferred upon it increased resistance to streptococci but this resistance was non specific and hardly greater than that conferred by sterile broth. They could not discover any growth-inhibiting factors in filtrates prepared by Besredka's method Re-inoculation of the organisms into the filtrates failed to produce cultures because of exhaustion of the medium, an occurrence already described and explained by Cobbett and Melsome (1895)

Rivers and Tillett (1925) found that the serum of rabbits, which had acquired localized skin immunity to the streptococcus protected normal rabbits against the development of erysipelas when it was injected into a skin area 24–48 hours before the streptococci but normal serum and even nutrient broth gave a similar though less powerful protection.

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...d Toomey (1928) carried out histological studies on guinea... ...d been subjected to compresses of sterile broth and was late...

inoculated with *Staph. aureus* Application of broth compresses for 48 hours produced localized oedema, great proliferation of histiocytes, and a moderate exudation of polymorphonuclear and small mononuclear cells. If *Staph. aureus* was injected after subsidence of the cellular reaction due to the compresses, there was a great outpouring of histiocytes and fibroblasts and of polymorphonuclear cells, which showed little tendency to degenerate. The histiocytes soon phagocytosed the staphylococci, and the fibroblasts began to wall off the lesion The same dose of staphylococci injected into an animal untreated with broth compresses caused great oedema, little accumulation of histiocytes or fibroblasts, and moderate accumulation of polymorphs, which rapidly degenerated. Owing to the absence of phagocytosis by histiocytes and of walling-off operations by fibroblasts, the lesion was much more diffuse and destructive than in broth-treated animals

It may be concluded from the foregoing studies that the increased resistance of the skin, after antecedent infection and inflammation, to subsequent infection is largely non-specific and is due to accelerated development of the normal inflammatory processes. In so far as this local immunity is specific, it depends upon the simultaneous production of a specific general immunity

DISINFECTION ON THE SKIN SURFACE

Schiemann and Landon (1919) were probably the first to call attention to the rapid disappearance of bacteria from the skin surface. They claimed that *Bacterium coli* deposited on the skin was not recoverable after a short time Dold and Chen Yü Hsiang (1919) pointed out that drying certainly and exposure to light probably help to destroy bacteria on the skin, and that gland openings, hair follicles, and other irregularities of the epidermis may trap organisms without killing them. This fact may lead to erroneous deductions in experiments designed to show the skin's disinfectant power by recovering organisms deposited upon it.

In 1928 in the first of a series of papers dealing with self-disinfection of the skin Marchionini and his school adduced much evidence to suggest that the bactericidal power of a given skin area depends upon, or varies with, its degree of acidity (Marchionini, 1928 1929 Schade and Marchionini, 1928a, b Marchionini and Cerutti, 1932 Marchionini, Schmidt, and Kiefer 1938)

Singer and Arnold (1929), Arnold *et al* (1930), and Karns and Arnold (1931) published a number of studies dealing with the self-disinfective power of the body surfaces. According to them, many common micro-organisms, such as *Erythrobacillus prodigiosus Staph. aureus, Bacillus pyocyaneus* (*Pseudomonas aeruginosa*) and *Bact coli* rapidly vanished f om the living, but not from the dead, skin.

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Norton and Novy (1931 1932) studied the rate of disappearance of *Erythrobacillus prodigiosus* from different surfaces, such as living skin, leather paper and glass They concluded that the death of organisms on these surfaces is due to

path of lymph drainage from the skin area first infected Other neighbouring areas were not protected against streptococci injected into them. The whole skin, after many injections of organisms into one area, acquired some anti-streptococcal immunity but this generalized skin immunity was accompanied by the development of humoral immunity evidenced by the appearance of antibodies in the blood

These observations, except those of Gay and Rhodes, show that localized immunity can be conferred by previous infection of a skin area with streptococci, but that immunity over the whole skin is only acquired concurrently with generalized humoral immunity

The mechanism of resistance

What is the mechanism of this local increase of resistance to re-infection of the skin?

Cobbett and Melsome (1898) pointed out that a local inflammation of a rabbit's skin induced by injecting mustard oil effectively protected the injected area against subsequent inoculation with erysipelogenic cocci. This protection was strictly local and these authors believed that it consisted in the greater speed with which the processes of inflammation such as the dilatation of vessels and the bringing up of phagocytic cells and antibodies, followed a second stimulus as the result of the practice acquired from the first.

Besredka and his colleagues (1923 1924) claimed that local immunization of the skin of rabbits could be effected by intracutaneous inoculation or poulticing of a skin area with bacterial filtrates that is, the broth filtered off from growths of streptococci or staphylococci They thought that these filtrates acquired properties toxic to the organisms, because growth no longer occurred in the filtrates on re-inoculation

According to Mallory and Marble (1925) filtrates from cultures of streptococci and staphylococci injected into the skin of rabbits some hours before infection of the area with streptococci, conferred upon it increased resistance to streptococci but this resistance was non-specific and hardly greater than that conferred by sterile broth. They could not discover any growth-inhibiting factors in filtrates prepared by Besredka's method. Re-inoculation of the organisms into the filtrates failed to produce cultures because of exhaustion of the medium, an occurrence already described and explained by Cobbett and Melsome (1895)

Rivers and Tillett (1925) found that the serum of rabbits, which had acquired localized skin immunity to the streptococcus, protected normal rabbits against the development of erysipelas, when it was injected into a skin area 24–48 hours before the streptococci but normal serum and even nutrient broth gave a similar though less powerful, protection.

Amoss and Bliss (1927) noted that a skin area which had recovered from erysipelas w[as] resistant to subsequent infection not only with the original erysipelogenic stra[in], but with other streptococcal strains and even with *Staphylococcus aureus*

Freedlander and Toomey (1928) carried out histological studies on guinea pigs skin which had been subjected to compresses of sterile broth and was later

inoculated with *Staph. aureus*. Application of broth compresses for 48 hours produced localized oedema, great proliferation of histiocytes, and a moderate exudation of polymorphonuclear and small mononuclear cells. If *Staph. aureus* was injected after subsidence of the cellular reaction due to the compresses, there was a great outpouring of histiocytes and fibroblasts and of polymorphonuclear cells, which showed little tendency to degenerate. The histiocytes soon phagocytosed the staphylococci, and the fibroblasts began to wall off the lesion. The same dose of staphylococci injected into an animal untreated with broth compresses caused great oedema, little accumulation of histiocytes or fibroblasts and moderate accumulation of polymorphs, which rapidly degenerated. Owing to the absence of phagocytosis by histiocytes and of walling-off operations by fibroblasts, the lesion was much more diffuse and destructive than in broth-treated animals.

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desiccation and that living skin is not superior to other surfaces in bactericidal power This view was disputed by Arnold and Bart (1934) who showed that a number of common organisms were still viable after they had been desiccated on cellulose fibres and then removed with alkaline phosphate solutions, whereas scrapings from living skin a few minutes after organisms were deposited upon it, failed to yield growth in culture media though specifically antigenic proteins of the organisms could be detected in the scrapings. They made the interesting observation that the sterilizing ability of the skin was enhanced by putting the subjects on a ketogenic diet, and believed that the acid reaction of the skin was important in self-disinfection

Cornbleet and Montgomery (1931) and Cornbleet (1932a and b 1933a and b), examined the problem of self-disinfection of the skin against yeast cells and *Staph. aureus* in normal persons and diabetics. They confirmed the existence of sterilizing power on the skin surface, but contested the view of Marchionini that this power is due to the acidity of sweat (For further discussion of this point, see p. 164.)

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I published some observations (Burtenshaw 1938) which convinced me that haemolytic streptococci but not a strain of *Staph aureus* placed on the palm and fingers perish more rapidly than on the forearm or on control surfaces, such as dead skin and glass, and that although drying undoubtedly plays a part in killing streptococci there is also at work some other agent, which is more destructive on those areas of the skin which possess a higher surface acidity

A novel theory of the reaction of skin to changes of *p*H has been propounded by Arnold (1942) He argues that the horny layers behave like a gel which on acidification contracts, imprisoning the endogenous flora while the increased hydrogen ion destroys any susceptible bacteria. On alkalization it swells by absorbing water and becomes more porous, so that imprisoned bacteria escape to the surface.

Bergeim and Cornbleet (1943) are satisfied that the lactic and volatile fatty acids of sweat, by reason of their acidity and perhaps of some specific action, act as mild skin antiseptics while recently Bancroft (1944) has correlated the disappearance of certain ringworm infections of childhood with the increased acidity and sebum production of the skin after puberty

Viruses as well as bacteria are destroyed by exposure on the skin. Krueger *et al* (1942) reported more rapid inactivation of influenza virus on the palm of the hand than on control surfaces, but did not suggest a mechanism of the process, which is perhaps adumbrated in the experiments of Stock and Francis (*see* p 173). Parker and MacNeale (1944) however found that the virus might persist for nearly an hour on the pa[illegible]m. They explain the discrepancy between their results and those of Krueger by the difference of virus strain and by the possible presence of traces of soap on the han[illegible]ds of Krueger s subjects.

From the work so far summarized it appears that the following factors contribute to the activity of the skin in ridding itself of organisms falling upon it (1) desquamation and certain physico-chemical properties of the epidermis (2) desiccation (3) acidity of the skin (4) the presence of fatty acids (5) the action of certain ill-defined bactericidal agents. Factors (3), (4) and (5) are considered further below

THE QUESTION OF THE REACTION OF THE SKIN SURFACE AND OF THE SKIN SECRETIONS

In 1848 Andral remarked *Ainsi, la peau sécrète deux matières de réaction différente l'une acide c'est la sueur l'autre alcaline c'est la matière sébacée Quelles que soient les conditions de santé ou de maladie dans lesquelles j'aie examiné la sueur je l'ai trouvée le plus ordinairement acide quelquefois neutre et jamais alcaline* His reason for supposing sebum to be alkaline was that he believed that alkaline regions of the skin, such as the nose or armpits, owed their alkalinity to the numerous sebaceous glands present in them or in the case of the armpits, believed to be present in them.

Gillibert d'Hercourt (1852) and soon after him Favre (1852), recorded by means of indicators that heat sweat in man is initially acid, but becomes alkaline after secretion has continued profusely for over an hour Favre observed *On a remarqué que la partie acide de la sueur perdait dès les premières gouttes vaporisées sa réaction acide qui faisait place à une réaction fortement alcaline* This observation suggests that there is present in sweat an acid component which rapidly volatilizes. Robin (1874) confirmed these findings for pilocarpine sweating.

Trümpy and Luchsinger (1878) maintained that human sweat is normally alkaline. They seem to have been biased towards this view by previous work of Hermann and Luchsinger (1877), which proved the invariable alkalinity of sweat from the cat's paw Using pilocarpine as diaphoretic and litmus paper as indicator they observed initial acidity on the skin of the face of man which later became and remained alkaline. If the skin was previously cleansed with fat solvents, the skin of the face was alkaline from the beginning of sweating. They chose to interpret these facts as showing that sebum provides the resting skin with an acid coat, which is forthwith washed away by alkaline sweat. Yet in experiments on the palm of the hand, which is free from sebaceous glands, they noted that the skin reaction was initially acid, but became alkaline as soon as pilocarpine sweating began. Their findings lend themselves to the alternative explanation, which they mention only to reject, that the normal sweat of the face and hand is acid, and that it becomes alkaline through excessive dilution due to the pilocarpine diaphoresis.

Most later work has demonstrated the acidity of human sweat. Thus François Franck (1884) and Kittsteiner (1911 1913), who first carried out titrations on the sweat stated that palmar sweat, which cannot be contaminated with sebum owing to the lack of sebaceous glands, was acid. Though a few investigators—for example Argutinsky (1890) and Camerer (1901)—have reported variable results, Talbert (1919) using chemical indicators and the hydrogen electrode, appears to

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have decided finally the problem of sweat reaction. He showed that, after cleansing the skin with fat solvents to remove sebum the sweat produced by heating in a closed chamber had a pH of from 5 32 to 5 22, and that the sweat produced by work on the bicycle ergometer with the body naked in a closed room had a pH of from 6·63 to 5·96 Talbert expressed himself as puzzled by the higher acidity of heat sweat in a later paper (1922) he showed that the different conditions, to which the skin was exposed in the heat and work experiments, were responsible for the anomaly In the heat experiments the subject was in a closed chamber in the work experiments in a large room If in both classes of experiment the subject was encased in a rubber sweat-collecting jacket, there was little disparity in the sweat reaction indeed the sweat resulting from work was always slightly more acid than that resulting from heat For example the heat sweat from the covered leg had a pH of 5 51 the work sweat a pH of 5·48 Talbert also found variations in the reaction of sweat from different parts of the skin surface thus heat sweat from the face had a pH of 5 99 from the leg a pH of 5·51

Adolph (1923) who compared the reaction of heat sweat with Sörensen's phosphate standards by means of indicators found that its pH when it was collected in beakers applied to the skin of the trunk varied from 6·5 at the start of sweating to 7 1 at the end of 30 minutes. Sharlitt and Scheer (1923) applied indicators directly to the skin of the cubital fossa immediately after thorough cleansing with fat solvents and with soap and water They found for this area of skin in 85 persons an average pH of 5 5 Mennesheimer (1924) placed drops of various indicators on the skin he concluded from observations on 100 normal subjects that the average pH of the skin surface is from 5 2 to 5·8

Schade and Marchionini (1928a) and Marchionini (1928) determined the reaction of the skin by indicators and by various electrometric methods. Using a hydrogen electrode inside a gas-chamber applied to the unwashed skin, they found a surface reaction on the living arm of about pH 3 8 and on the corpse of about pH 3 5 Sweat from the eccrine glands which discharge over far the greater part of the body surface, had a pH of 3 8–5·6 sweat from the apocrine glands, which only develop at puberty and open into the hair follicles of a few regions, such as the axillae and the perineum (Schiefferdecker 1922) had a pH of 6 2–6·9 Other parts of the skin not supplied by glands anatomically apocrine, such as the forehead the naso-labial folds, the interdigital regions and the soles of the feet, were more alkaline after than before puberty They accounted for the skin surface being more acid than sweat by explaining that sweat is continually becoming more concentrated on the skin owing to evaporation If the reaction of the skin was measured during the onset of sweating in a light-bath, there was at first a rather sudden drop in acidity caused by the dilution of the concentrated sweat on the skin by an outpouring of more dilute sweat then there was a further more gradual drop due to escape of the more volatile sweat acids. If sweating now ceased, the skin acidity gradually rose towards its resting level as the concentration of the freshly secreted sweat proceeded. Sweat, either artificially collected or allowed to stagnate on the skin gradually became alkaline—a change ascribed by Marchionini to the action of micro-organisms. By pressing his electrodes into the depths of the skin Marchionini determined the pH of the

different layers In the corpse it fell gradually from 7·00 to 3·29 in the living subject from 7 50 to 3·34 in passing from the cutis towards the surface.

In a paper apparently read before a meeting of dermatologists, Brill (1928a) asserted that the greater alkalinity of eczematous skin should probably be attributed to lack of sebum, and he quoted the work of Trümpy and Luchsinger in support of his view Yet in another passage he declared that eczematous persons sweat less than do normal people, and that pilocarpine induces less sweating in the eczematous subjects than in controls. Marchionini took part in the subsequent discussion. He opposed Brill in his opinion that sebum, rather than sweat, is the acidifying agent of skin. In a later paper (1928b) Brill admitted that sebum is only one factor in the production of skin acidity

Vass and McSwiney (1930) confirmed Marchionini's statement that sweat becomes alkaline on standing. Sweat initially at pH 5·95 had a reaction of pH 7 70 at the end of 66 hours at 37° C. and the ammonia in it rose from 3 8 to 37·6 milligrams per cent. The changes in composition were caused by bacterial activity if the sweat was passed through a filtering candle before it was allowed to stand, they did not occur Perutz and Lustig (1931) amplified Marchionini's work by noting that the acidity of the finger skin, normally at a pH of about 5 3 temporarily fell after removal of the surface layers of the skin, but rose remarkably soon to its previous level. Mosher (1932) corroborated the measurements of Marchionini he found that eccrine sweat, collected from well-washed skin on rubber sheets, varied in reaction between pH 5·42 and 5·91 If apocrine sweat was not excluded, then the pH might rise to 8·4. He believed that many of the discrepancies in measurements of sweat reactions were caused by failure to differentiate between these two kinds of sweat. In the same year Fishberg and Bierman (1932) estimated at pH 4 0–4 5 the reaction of sweat collected from the whole body also Marchionini and Ceruttí (1932) extended their work on skin acidity by mapping out with the chinhydrone electrode and a gas chamber the pH values of almost every region of the human skin. On skin moist with moderate sweating these values varied from pH 6·0 to 4·0, on dry skin from pH 5·0 to 3·0. Mosher's belief mentioned above, is supported by the work of McSwiney (1934) who recorded that the pH of specimens of heat sweat from 14 young men varied between 5·10 and 7 35 and that the pH of seven specimens from the same subject varied between 5·10 and 6·20 Whitehouse (1935), employing the British Drug Houses capillator method, determined the pH of sweat obtained from the washed back and leg as 4·6–5·0 but that of face and armpit sweat as 7·0. Hoff (1935), too, obtained values of pH 7 2–6·2 and pH 7·6–6·9 for the reaction of forehead and of armpit sweat respectively Thus both Whitehouse and Hoff corroborate Marchionini's (1928) finding of the alkalinity of forehead skin.

In a later series of papers Marchionini and his colleagues (Marchionini and Hausknecht, 1938 Marchionini 1938) delineate more exactly the gaps in the acid mantle of the skin. To the more alkaline areas already mentioned they now add the *vordere und hintere Schweissrinnen* namely the strips of skin stretching from manubrium sterni to pubis and from the spines of the lower cervical vertebrae to the gluteal cleft. The skin of the flexures—for example in the inguinal and gluteal regions, under the female breasts, and between the scrotum and thighs—

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29·8° C. 8·9 grammes, and at 38·4 C. 29·5 grammes of carbon dioxide were eliminated in 24 hours through the skin.

In Talbert's experiments (1919) any CO_2 in sweat was certainly not responsible for the observed acidity because equalization of gas pressure between air and sweat was allowed before *p*H estimations were carried out. Moreover Talbert (1922) collected sweat with precautions against CO_2 escape, and failed to obtain from the fluid by Van Slyke's method significant amounts of the gas but on his finger placed over the top of a tube containing sweat he collected an acid condensate. He interpreted this result by postulating the evaporation of volatile acids, not CO_2, from the sweat. It does not seem, however that he prevented his finger skin from acidifying the condensate. He furnished a more reliable indication of the presence of volatile acids in sweat by finding that sweat from rubber jackets was more acid than sweat openly collected on rubber sheets. Recently Piper (1943) has demonstrated that a portion of the titratable skin acid is furnished by CO_2.

Acids of the sweat and of sebum

Sharlitt and Scheer (1923), after determining, as already mentioned, an average *p*H of 5·5 on the skin, argued that this degree of acidity could hardly be conferred by the sebum or sweat of skin so recently cleansed, and that it is reasonable teleologically that the collagen and keratin of the skin should be kept at the *p*H at which they are most stable that is to say at their iso-electric point. They quoted the observations of Thomas and Kelly (1922), who gave the iso-electric point of the corium collagens as *p*H 5·0. This argument lucidly explains why it is desirable that the skin should be maintained at a *p*H of about 5·0 but it fails to explain the mechanism of this maintenance. Now Talbert's figure for the reaction of heat sweat was about *p*H 5·5 which is the average figure found by Sharlitt and Scheer for the reaction of the skin surface. It therefore seems probable that, in spite of the most thorough cleansing, acids of the sweat and sebum remain fixed in the superficial layers of the skin and preserve its acidity (Viersler 1940) Yet Jacobi (1942) contends that the skin acidity is maintained by breakdown products of the keratin layers.

Unna and Golodetz (1909) analysed fat obtained from the skin its appendages and its secretions. According to them sebum contains 44·9 per cent water insoluble fatty acids with an acid number of 202, sweat-gland fat from the soles, 59·7 per cent fatty acids with an acid number of 188 and fat from the horny layer of the epidermis, 54·75 per cent fatty acids with an acid number of 181·5. Later Unna (1913) recorded that lactic acid and the volatile fatty acids, formic, acetic, butyric, and caproic, are present in sweat.

Lactic acid

In a comprehensive review of the skin secretions, Schwenkenbecher (1929) stated that lactic acid is mainly responsible for the reaction of sweat, with the help of other acids, such as formic, acetic, butyric, propionic, caproic, caprylic, derived probably from decomposed sebum (Knerdl) and traces of sulphuric and phosphoric acids. Fishberg and Bierman (1932) found lactic acid in sweat in amounts of 250–350 milligrams per cent. They considered the acid responsible for the sweat reaction (*p*H 4·0–4·5). Chatron (1933) estimated by the Godfon-Nepreux technique that the total organic acids in 100 cubic centimetres of sweat were

where evaporation is slow and decomposition of sweat favoured also possesses a less than average acidity Diseases of the skin alter its reaction Atrophic lesions, scurf producing and blister producing processes (psoriasis, eczema, etc.) and chronic inflammations (acne vulgaris) lead to increased alkalinity of the affected areas (*p*H 8 3–5 8) whilst the blister fluid in true dysidroses and the pus of acute inflammations (boils) is acid (*p*H 5 8–4 8) The greater alkalinity of diseased skin had been noted earlier by Perutz and Lustig (1931) and by Levin and Silvers (1932)

Finally the recent work of Blank (1939a b) of Pillsbury and Shaffer (1939) and of Draize (1942) must be considered Blank concluded that the skin is well buffered from the fact that unbuffered fluids ranging from *p*H 4·0 to 9 7 applied to it made little difference to subsequent *p*H measurements of the surface. The areas of skin investigated by him had a reaction lying between *p*H 7·0 and 4·0. The antecubital fossa was most acid, and next in order of acidity came the forehead which Marchionini and others had pronounced alkaline. Whereas boys skin became more acid at puberty there was no pubertal change in the case of that of girls. Women s skin at menstruation showed an alkaline or acid shift of *p*H constant for the individual and greater daily variations of *p*H than that of men.

Pillsbury and Shaffer confirmed the work of Marchionini and others on the regional differences of skin reaction and by fixing inverted cups containing buffer solutions on to the skin surface, they discovered that it could withstand for a short time without damage hydrogen and hydroxyl ion concentrations ranging between *p*H 2·0 and 12 6 Draize using a glass electrode similar to Blank s, found the lowest *p*H (4·04) on the back of the upper arm of a white male, and the highest (6 66) on the back of the hand of a white female The average of *p*H estimations on the antecubital fossa was the lowest of the averages for all the skin areas examined this finding corroborates that of Blank.

From this review of past research on the reaction of human skin it may be concluded that

(1) the skin over most of the body surface is normally acid (about *p*H 5·0) except in areas furnished with apocrine sweat glands

(2) the sweat is capable of producing the reaction of the skin areas upon which it is secreted though probably the sebum contributes to this acidity

THE SUBSTANCES FORMING PART OF OR EXCRETED THROUGH, THE SKIN WHICH CONFER ACIDITY UPON IT

Foster (1889) remarked We are not able, at present to make a complete statement as to what bodies occur exclusively in the sebum and what in the secretion of the sweat glands. The former consist very largely of fats and fatty acids, and appear to contain some form or forms of proteids but we have reason to think that the sweat glands secrete in small quantity some forms of fat and especially volatile fatty acids.

Carbon dioxide

Many authors, for instance Aubert (1872) Röhrig (1872) Fubini and Ronchi (1881) Schlerbeck (1893) have noted the excretion in the sweat of carbon dioxide and its possible influence on the skin reaction. Thus Schlerbeck found that at

few attained pH 4·8, before death of the organisms under similar conditions (1919b) *Str pneumoniae* in presence of ample glucose might reach pH 5·0, but in the absence of glucose only pH 7 8 Working with white and yellow staphylococci, obtained from various lesions, and from the nose and urine, Hall and Fraser (1921) determined the limits of pH allowing growth in broth as 4·6–10 0 Dernby (1921), investigating a number of common bacteria, found that the lower pH limit for growth in broth of the pneumococcus was 7·0 for *Staph. aureus* and *Staph. albus*, 5·6 for *Bact typhosum* 6·2, but for *Bact paratyphosum B* and *Bact coli* 4·5 for *Coryn. diphtheriae* 6·0 for *B anthracis* 6·0 but for *B subtilis* 4 5. Eggerth (1926) in agreement with Avery and Cullen, noted that exposure for 2 hours in saline buffer solution at pH 5·5 killed *Str pyogenes*

Because Marchionini (1928, 1929) found that the pH of many parts of the skin surface varies between 3·0 and 5 0 and ascribed the disinfectant action of skin to its acidity I assayed the effect of acidity on the strains of streptococcus used in my own experiments (Burtenshaw 1942). There was always a progressive fall in the number of organisms recovered within a given time from normal saline (0·85 per cent) through the pH range 7 5–5·0 the fall in recovery rate fell, as a rule, more steeply below pH 5 0

The above figures indicate that the degree of acidity commonly found on the skin would suffice to kill several of the common pathogens, such as *Str pyogenes* and *Str pneumoniae Bact typhosum*, and *Coryn. diphtheriae*

THE LIPOIDS OF THE SKIN AND ITS APPENDAGES AND THEIR ROLE IN AUTOGENOUS DISINFECTION

As Viertaler (1940) points out, the fats protect the skin mechanically by keeping it supple and by preventing the formation of cracks and crevices in which organisms may lodge and multiply The question whether the skin fats or their components might have a bactericidal function was suggested to me by the work of Brann (1928), who discovered that viable organisms were but sparsely present in human and animal hair and that the fats extracted from it with ether were lethal to several common bacteria. I had already found (Burtenshaw 1938) that *Str pyogenes* disappears more rapidly on the skin of the hand than on control surfaces, and a few preliminary experiments (Burtenshaw 1942) convinced me that the acidity of skin scrapings would not alone account for this difference. Could the fats contribute in any way to the sterilizing power of skin? To answer the question I prepared ether and alcohol extracts of skin, hair cerumen, and nails, and tested them, after removal of the solvents and suspension in saline, against a number of common bacteria, mainly several strains of *Str pyogenes* The extracts were found to be strongly bactericidal to *Str pyogenes Str viridans* and *Coryn. diphtheriae* but harmless to *Bact coli* and *Bact typhosum*. Some strains of *Staph. aureus* and *Staph epidermidis albus* were partly sterilized, others were unaffected.

On splitting up hair fat into several fractions, that comprising the fatty acids was alone streptococcidal, and it may be assumed that these substances endow the other skin fats with disinfectant power That these acids have long chains is supported by their low volatility and high ether-water repartition ratio and by the

equivalent to 15–18 cubic centimetres of N/10 acid. According to McSwiney (1934) lactic acid varies between 34 and 100 milligrams per cent (Talbert, Mosher Vass) in the sweat of persons at rest or doing moderate work in the sweat of those doing hard work for example, Marathon runners, it may rise to 1 765 milligrams per cent (Kosikiana and Kristonnikoff)

Whitehouse (1935) found that resting sweat from persons kept at 95° F in a moist atmosphere contained 70–113 milligrams of lactic acid per cent but he concluded from experiments on the leg, such as the following, that sweat is not responsible for skin acidity The subject was exposed for 20 minutes in a hot-air bath at 95° F., and the pH of the sweat collected at the end of this period was 4 7 If the skin was then thoroughly washed the pH of the sweat rose a few minutes later to 5 9 A few minutes after a second wash the pH of the sweat rose to 6·4 and a few minutes after a third wash to 7·00 He interpreted these observations as meaning that skin acidity was conferred by traces of acids, such as lactic or sulphuric, formed on the skin surface and removable by repeated cleansing but *he did not cite any control experiments to prove that the acidity of the sweat would* not have fallen similarly without interpolated washings in the same period (nearly an hour) of continued sweating. *Without such a control Whitehouse s experiment* signifies nothing for many workers such as Favre and Talbert have noticed that the pH of sweat increases with the duration of sweating Again in support of his notion that sulphuric and lactic acids are formed on the surface of the skin, he emphasized that the ratio of these acids to chloride in washings from the skin is much higher than the corresponding ratio in the sweat of early diaphoresis. But it may well be that the proportions of these acids and of chloride found in skin washings are those existing in evaporated resting sweat this supposition is strengthened by Whitehouse s own demonstration that the ratio of lactic acid to chloride falls as sweating becomes more copious.

A meticulous analysis by Couraud (1935) of the acids of sweat revealed that 75 per cent of the ether-soluble (that is, organic) acids of sweat is lactic the remaining 25 per cent consists almost entirely of volatile acids and of a small proportion varying *between 8·0 and 0·5 per cent, of non volatile acids.* The lower members of the acetic series, which are distillable in steam and of which several *have been recovered from sweat* (Unna, 1913) may well be constituents of this volatile fraction. In 4 samples of sweat, collected entirely from the trunk, there was among the organic acids a non volatile fraction amounting to about 25 per cent contributed perhaps, by the apocrine glands of the axillae and perineum (Schiefferdecker 1922) by the oleic acid derived from the desquamating epidermis (Unna, 1928) and by the sebum, which contains fatty acids of *relatively high* molecular weight (Cerutti 1934)

It is justifiable to conclude from this brief review that the substances responsible for skin acidity are, in order of importance, lactic acid, a number of fatty acids of the acetic series, carbonic acid and possibly *breakdown products of keratin.*

THE EFFECT OF ACIDITY ON THE VIABILITY OF ORGANISMS

Avery and Cullen (1919a) observed that most human strains of *Streptococcus pyogenes* growing in 1 per cent glucose broth attained pH 5 3–5·0 and that a

Dermocerin and was found by Ameseder (1907) to consist largely of eikosyl alcohol ($C_{20}H_{41}OH$). Sebum also contains some soaps (von Ziemssen, 1883). Recently Melczer and Deme (1942) have claimed that the lipoid in the ducts of sebaceous glands and in hair follicles is mainly neutral fat and fatty acids. The ceruminous glands, though homologous with the sweat glands (Quain, 1912 Testut, 1922), produce a secretion resembling sebum (Linser 1904 Unna and Golodetz, 1909 Schwenkerbecher 1929).

Compared with the secretion of the skin glands, the fat of the epidermis and nails is rich in cholesterol and its esters, amounting in these structures to 16 per cent of the lipoids (Unna and Golodetz, 1909). From the appearances after staining with osmic acid, Unna (1928) inferred that oleic acid and its esters are *die eigene Fett der Hornschicht* By staining methods Koga (1934) demonstrated the presence of fatty acids and their soaps and esters in the horny skin, whilst Partridge (1938) concluded that the epidermis contains numerous highly unsaturated hydrocarbons. Eckstein and Wile (1926) found that about 2·5 per cent of epidermal fat is phospholipoid, which, being easily hydrolysable and containing a large proportion of unsaturated fatty acids (Kooyman, 1932), may well be an important source of unsaturated acids. Much of the fat normally present on and in the superficial layers of the skin is derived mainly from the sebum and in very small amount from the sweat (Schwenkerbecher 1929 Cerutti, 1934) but Unna held that part is produced by the keratinization process.

About 4 per cent of hair is lipoid, of which only 3 per cent is embodied in the hair the rest is absorbed sebum (Cerutti, 1934). According to Eckstein (1926) of the 4·5 per cent total fat in rats hair 11·9 per cent consists of cholesterol and 0·86 per cent of lecithin.

In brief fat from nails and the palmar skin, where there are no sebaceous glands, contains oleic and other unsaturated acids with their esters and soaps together with traces of short-chain fatty acids, whereas fat from hair and cerumen and from far the greater part of the skin, which is supplied with sebaceous glands, contains numerous long-chain and short-chain fatty acids with their esters and soaps, derived from, or characteristic of, sebum.

I attempted a rough analysis of fat extracted from human hair (Burtenshaw 1942) and obtained the following figures

Total fat in hair — — —	5·46 per cent of hair
Unsaponifiable fraction — —	36·1 per cent of total fat
Water-insoluble fatty acids	63·9 per cent of total fat
Total acid number —	201·9
Iodine value of fatty acids	49·0
Cholesterol —	4·6 per cent of total fat
Phospholipoid —	1·5 per cent of total fat

These figures, compared with those given by Unna and Golodetz (1909) for various skin fats, suggest that the fat in ether extract of hair is a mixture of sebum and sweat lipoids together with some epidermal cholesterol. The iodine value agrees approximately with Linser's for sebum fat, namely 36–44 (Schwenkerbecher 1929) it indicates that more than half the acids are unsaturated, if oleic (iodine value = 90) is the chief unsaturated acid present.

proved bactericidal power of most long-chain acids and soaps, contrasted with the lack of this power among the short-chain acids and soaps.

My demonstration (Burtenshaw 1942) of the susceptibility of the streptococcus to oleic, stearic, lauric, and capric acids and their soaps, and of its resistance to the lower fatty acids and soaps, harmonizes with the findings of many workers, notably Lamar (1911) Nichols (1920) Walker (1924) Eggerth (1926) Bayliss (1936), and Belin and Ripert (1937)

Reichenbach (1908) Walker (1924) and Bayliss (1936) showed that members of the genus *Bacterium* are almost unaffected by the unsaturated soaps, but are susceptible to 1 per cent concentrations of the saturated soaps. Walker and Bayliss found *Staph aureus* very resistant to all soaps, but Hettche (1934) records destruction of this coccus by a number of unsaturated acids. Walker (1925) noted the extreme sensitiveness of *Coryn. diphtheriae* to oleates. The tubercle bacillus is peculiar in being more susceptible to the lower fatty acids, especially formic, than to the higher members (Hailer 1938) The results of these experiments on the action of soaps on members of the genus *Bacterium* on *Staph aureus*, and on *Coryn diphtheriae* conform with my observations of the effect of hair extracts on these organisms.

Certain fungi possess quite different susceptibilities to various fatty and hydroxy acids. Thus Peck and his colleagues (1939) found that 0·009 per cent caproic, 0·03 per cent propionic and caprylic, 0·2 per cent lactic, and 0·3 per cent citric and ascorbic acids sufficed to kill *Trichophyton gypseum* Longer-chain fatty acids were not tested Their work supports Hermann and Fürst's claim (1929) that sweat baths are beneficial in fungus infections of the skin.

What then are the fatty acids and acid yielding lipoids present in the skin, its appendages and secretions?

As described above (p 167), sweat contains small amounts of the fatty acids up to caprylic, partly derived from decomposed sebum (Schwenkerbecher 1929), and partly excreted in the sweat (François-Franck 1884 Unna 1913).

There has been much controversy about the secretion of lipoids by the eccrine sweat glands. Unna (1894 1898 1928) described droplets staining with osmic acid in the alveolar cells and ducts of sweat glands, and concluded that the[y]
oleic acid He also argued that as fat was detectable in the sweat of th[e]
sole and there are no sebaceous glands in these regions, the fat mu[st]
the sweat It was pointed out however by Rothman (1929) th[at]
with osmic acid are not necessarily oleic acid, that such dr[oplets]
the duct lumen of sweat glands—a fact recently chec[ked]
that the presence of fat on the palms and soles in
does not prove that fat is excreted in sweat
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ducts of eccrine sweat glands, and acc
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These proofs of the susceptibility of micro-organisms to fatty acids and soaps, and of the presence of these substances in and upon the skin, justify the conclusion that the acids and soaps contribute to the bactericidal power of the skin, though according to Eggerth (1927) and to Kodicek and Worden (1945) such substances as lecithin, and less strongly cholesterol may interfere with this activity of the fatty acids.

THE RELATIONSHIP OF *p*H TO SPECIFIC POWER IN THE BACTERICIDAL ACTIVITY OF THE FATTY ACIDS

Do the fatty acids kill micro-organisms merely through the toxicity of the *hydrogen ion or have they in addition some specific disinfectant power? In my* own work on the streptococcicidal action of hair fats (Burtenshaw 1942), it appeared that both fatty acids at *p*H 5·0–4·0 and soaps at *p*H 7·0–8·0 were more active than were saline controls at the same *p*H However though both the acid and its soap seem to possess specific activity this is greater for the acid than for the soap Mathematically expressed

$$(1)\ \frac{\text{Lethal action of soap } (pH\ 7{\cdot}5)}{\text{Lethal action of fatty acid } (pH\ 4{\cdot}5)} < (2)\ \frac{\text{Lethal action of saline } (pH\ 7{\cdot}5)}{\text{Lethal action of saline } (pH\ 4{\cdot}5)}$$

If the specific factor had the same value in the denominator as in the numerator of (1) then (1) would approximately equal (2) In fact (1) is less than (2) owing to the denominator of (1) being raised, presumably through an increased value of the specific factor

Eggerth (1926) who proved that the fatty acids are nearly always more lethal than their soaps to *Str pyogenes Staph aureus, Coryn. diphtheriae Vibrio cholerae* and *Bact typhosum* suggested four reasons for the greater effectiveness of the acids. (1) The acid reaction may sensitize the bacterium to the soap or fatty acid (2) *Decrease of pH in soap solutions lowers the surface tension* which leads to greater concentration of the soap or acid at the water–bacterium interface. (3) Coulter (1924) discovered that, if the acidity of a suspension of erythrocytes is raised the inside of the cells does not become as acid as the outside fluid If the same is true of bacteria it is likely that rising acidity in a soap solution would drive the increasingly insoluble soap into the more alkaline bacterial protoplasm. (4) The fatty acid molecule being less dissociated than the soap molecule, may penetrate more easily into the bacterium (Osterhout, 1925)

That a number of organic acids are more lethal than are their salts to certain fungi was shown by Peck *et al* (1939) on the other hand Lamar (1911) asserted that soaps are more effective than are their acids in killing the pneumococcus

THE MECHANISM OF THE BACTERICIDAL ACTION OF FATTY ACIDS AND SOAPS

It has long been known that the disinfectant power of many hydrocarbons and their ability to reduce surface tension increase with the length of their carbon chain. *This has been demonstrated for the alcohols by Wirgin (1904) Traube (1919)* Cowles (1938) and Kokko (1939) for the acids by Lamar (1911) and Reid (1932), and for the soaps by Bereczeller (1917) Walker (1924) and Stock and Francis (1940)

Yet lowering of surface tension is not alone responsible for the lethal action of these substances their water solubility and molecular constitution and the kind of organism acted upon also play an important part. As a rule unsaturated acids are more active than are saturated acids of comparable length of chain against the pneumococcus, streptococcus, and *Coryn diphtheriae* often this increased activity runs parallel with greater ability to lower surface tension than that of comparable saturated acids. Lamar (1911) pointed out that the long-chain unsaturated acids oleic ($C_{18}H_{34}O_2$), linoleic ($C_{18}H_{32}O_2$), and linolenic ($C_{18}H_{30}O_2$) and their soaps, with iodine values of 90 07 181-42, and 243 2 respectively fall in that order of increasing toxicity to the pneumococcus, and that the soaps, being more soluble, are more toxic than are the acids. Of all the acids and soaps tested, potassium linolenate showed the greatest toxicity correlative with its high iodine value, its long chain, and its great water solubility Crotonic acid ($C_4H_6O_2$), however though it has an iodine value of 295-28, has a short chain and is but slightly toxic also chaulmoogric acid with an iodine value of 90-3 an isomer of linoleic acid, is partly of ring structure and is less toxic than is oleic acid. Walker (1924 1925, 1926) found that *Str pneumoniae* and *Str haemolyticus Coryn. diphtheriae Neisseria meningitidis* and *Neisseria gonorrhoeae* are extremely susceptible to the oleates, linoleates and linolenates, but that the saturated laurates, perhaps because of their notable power of reducing surface tension, are as effective as the linoleates. Bayliss (1936) observed that 1·0 per cent sodium stearate, 0·1 per cent palmitate, 0 01 per cent myristate, 0 04 per cent laurate, 0 004 per cent oleate, and 0 005 per cent linoleate kill the pneumococcus in 15 minutes, but 0·03 per cent α-elaeostearate and 0·4 per cent β-elaeostearate (isomers of linolenate) are needed to kill it in the same time. Eggerth (1929a and b) found that hydroxyl or α-bromine increases the effectiveness of the saturated acids, but that α-hydroxyl decreases the effectiveness of the unsaturated acids, a finding confirmed by Bayliss (1936). Recently Kodicek and Worden (1945) have demonstrated the bacteriostatic action, increasing with the degree of unsaturation of oleic, linoleic, and linolenic acids on *Listeria helveticus* and other Gram-positive organisms such as *B anthracis, Staph. albus, L. monocytogenes*, and *Erysipelothrix rhusiopathiae* the Gram-negative *Bact. coli* and *Proteus vulgaris* were unaffected by the acids. Stock and Francis (1940), working with the influenza virus, noted that it is inactivated most strongly by the unsaturated acids with 18 carbon atoms in their chain oleic, linoleic, and linolenic. They emphasized that intensity of disinfection does not always vary with degree of unsaturation. Thus, chaulmoogric, undecylenic, pyromucic, and β-elaeostearic are almost inactive, whilst lauric and, less markedly myristic acids are active Ability to lower surface tension is very commonly but not invariably correlated with virocidal power For example undecylenic, ricinoleic, chaulmoogric, and palmitic acids powerfully depress surface tension but have little effect on the virus.

In contrast with *Str pyogenes* and *Str viridans*, with certain members of the genus *Neisseriae* with *Coryn. diphtheriae* and with the influenzal virus, the genus *Bacterium* is far more susceptible to the saturated than to the unsaturated acids and soaps (Reichenbach, 1908 Walker 1924 1926 Bayliss, 1936), though they withstand all these substances far better than does the group sensitive to unsaturated acids. According to Reichenbach, 1 per cent sodium palmitate acting for 50 minutes kills *Bact. coli*, whereas only 10 per cent oleate suffices to kill in the

same period. Walker obtained similar results with the typhoid and dysentery bacilli.

As mentioned above (p 170) *Staph aureus* is very resistant to most of the long-chain acids and soaps. Bayliss (1936) found 1 per cent laurate, abietate and undecylenate slowly effective, and Hettche (1934) recorded partial sterilization with 0·1 per cent oleate and complete sterilization with 0·1 per cent linoleate and linolenate in 60 minutes but none of the soaps used by Walker (1924) affected the staphylococcus.

From reviews such as those of Rideal (1923 1930) and of Harris and Bunker (1931) the action of long-chain alcohols, of fatty acids and of soaps on bacteria in a watery medium may be pictured as follows The molecules of these substances, owing to their water insoluble carbon chains, collect at the water–bacterium interface, where their OH NH_2 and COOH groups protrude into the water and their fat-soluble carbon chain is adsorbed to the partly lipoid envelope of the bacterial cell. By intercalating themselves between the surface molecules, they effect a marked difference between the surface tension of the outside and the inside of the cell envelope which undergoes peptization that is, disruption. Even if the cell is not destroyed, active groups of the lipoid such as OH and COOH, combine with active groups of the cell surface and impede its chemical exchanges, whilst peroxides may form round unsaturated linkages in the lipoid or in such groups as —CHO and =CO and disorganize the protein metabolism

Kodicek and Worden (1945) discussing the bacteriostatic effect of long-chain unsaturated fatty acids on *L. helveticus* conclude that the acid molecules alter the permeability and surface tension of the cell membrane, thus retarding cell division and perhaps interfering with bacterial metabolism. They suggest that substances such as cholesterol calciferol, and lecithin annul the action of these acids by forming complexes with them and withdrawing their active groups from the cell surface.

It is curious that no other long-chain molecules in skin fat besides the fatty acids—for example, esters and alcohols—evince streptococcicidal power It is likely that the active groups of the component parts of the esters are largely neutralized by internal combination furthermore the alcohols of skin fat are, according to Ameseder (1907) mainly of the type of eikosyl alcohol ($C_{20}H_{41}OH$), which has a very long chain and but a single hydroxyl group Both esters and alcohols, therefore, must be nearly insoluble in water and chemically almost inert. Eggerth (1926) found that in a homologous series of saturated soaps the sterilizing power for various organisms reaches its peak in the member containing 12 or 14 carbon atoms and falls away rapidly in the higher members A similar peak may well exist in an alcoholic series

OTHER FACTORS OF POSSIBLE IMPORTANCE IN AUTOGENOUS DISINFECTION OF THE SKIN

At various times since the days of Hippocrates and Galen investigators have re-awakened interest in the possible existence of a poisonous substance excreted upon or emanating from the skin of menstruating women.

Such a substance, supposed not only to be bactericidal, but to cause flowers to wilt and fermentation processes to alter their course, was described by Schick (1920) and named by him, after von Groer menotoxin He ends his paper on a note of triumph *Ich aber sage wir sollen uns freuen, dass dieser Glaube nicht ausgerottet ist, wir sollen dem Volke dankbar sein, dass es an solchen durch mündliche Überlieferung fortlebenden Tatsachen zähe festhält!* This enthusiastic vindication of folk-lore has not been upheld by others. Neither Sänger (1921) nor Gengenbach (1925) could produce evidence to support it, and Rothman (1929) remarks that menotoxin is now considered a myth. Fisher (1931) tested the power of the hand skin of menstruating women to kill *Bacillus prodigiosus*, and in some cases repeatedly found a decrease of this power during the period. She makes no mention of menotoxin indeed it is probable that the decrease of disinfectant power depends on a fall in skin acidity during menstruation (Blank, 1939b).

Fleming (1922, 1929 1932) described a substance, called by him lysozyme which is present in varying amounts in most animal tissues. It is present in skin, hair and sebum, but not in sweat. Recent researches by Roberts (1937), Abraham and Robinson (1937), and Epstein and Chain (1940) indicate that lysozyme is a protein of low molecular weight with the properties of a polysaccharolytic enzyme. It is lytic in very high dilution to a coccus recovered from nasal mucus and christened by Fleming *Micrococcus lysodeikticus* but it is also active against many different organisms, including the streptococci. It is inhibited, but not destroyed, by minute additions of acid or alkali, so that it would be inactivated on most areas of the skin. It is questionable whether Fleming in his studies was always dealing with the same lysin. Tears and egg albumin were the sources chiefly used in determining the properties of lysozyme, and it was assumed that the same substance was responsible for the lytic activity of skin, hair and nails. In the light of Brann s (1928) and my own work (1942) the activity of these structures may with greater likelihood, be attributed to fatty acids and soaps.

Hill and White (1933) applied their finger-tips to the surface of a blood-agar plate, in which haemolytic streptococci had just been incorporated. After incubation they found colonies growing throughout the medium except under and for a short distance around, the surface area touched. They tentatively ascribed the inhibition to a lysin, such as Fleming's lysozyme, diffusing into the medium from the skin. Using my own finger-tips, I was quite unable to repeat this observation of Hill and White (Burtenshaw 1938) but they admitted that a small proportion of their subjects failed to inhibit streptococcal growth.

Gaube (1891) established the existence of traces of amylase and pepsin in human sweat and in horse sweat Ottenstein (1931) investigated the variations in the diastase content of skin and sweat. Though it is conceivable that these enzymes may play a defensive role, no such idea was mooted by these authors but Tzank (1936) mentions a skin lipase which is active against *Myco tuberculosis* and *leprae* in the epidermis.

Many workers, including Wren (1927), Harris, Bunker and Milas (1932), Sears and Black (1934), and Stevens (1935, 1936a, b, and c), have reported the formation in vegetable and mineral oils on exposure to oxygen and ultra-violet light of volatile

same period Walker obtained similar results with the typhoid and dysentery bacilli

As mentioned above (p 170) *Staph aureus* is very resistant to most of the long-chain acids and soaps Bayliss (1936) found 1 per cent laurate, abietate and undecylenate slowly effective, and Hettche (1934) recorded partial sterilization with 0·1 per cent oleate and complete sterilization with 0·1 per cent linoleate and linolenate in 60 minutes but none of the soaps used by Walker (1924) affected the staphylococcus.

From reviews such as those of Rideal (1923 1930) and of Harris and Bunker (1931) the action of long-chain alcohols, of fatty acids and of soaps on bacteria in a watery medium may be pictured as follows. The molecules of these substances, owing to their water insoluble carbon chains, collect at the water–bacterium interface, where their OH NH_2, and COOH groups protrude into the water and their fat-soluble carbon chain is adsorbed to the partly lipoid envelope of the bacterial cell. By intercalating themselves between the surface molecules, they effect a marked difference between the surface tension of the outside and the inside of the cell envelope, which undergoes peptization that is, disruption. Even if the cell is not destroyed active groups of the lipoid, such as OH and COOH, combine with active groups of the cell surface and impede its chemical exchanges, whilst peroxides may form round unsaturated linkages in the lipoid or in such groups as —CHO and =CO and disorganize the protein metabolism.

Kodicek and Worden (1945) discussing the bacteriostatic effect of long-chain unsaturated fatty acids on *L. helveticus* conclude that the acid molecules alter the permeability and surface tension of the cell membrane thus retarding cell division and perhaps interfering with bacterial metabolism. They suggest that substances such as cholesterol calciferol, and lecithin annul the action of these acids by forming complexes with them and withdrawing their active groups from the cell surface.

It is curious that no other long-chain molecules in skin fat besides the fatty acids—for example, esters and alcohols—evince streptococcicidal power It is likely that the active groups of the component parts of the esters are largely neutralized by internal combination furthermore, the alcohols of skin fat are according to Ameseder (1907) mainly of the type of eikosyl alcohol ($C_{20}H_{41}OH$), which has a very long chain and but a single hydroxyl group. Both esters and alcohols, therefore, must be nearly insoluble in water and chemically almost inert. Eggerth (1926) found that in a homologous series of saturated soaps the sterilizing power for various organisms reaches its peak in the member containing 12 or 14 carbon atoms and falls away rapidly in the higher members. A similar peak may well exist in an alcoholic series

OTHER FACTORS OF POSSIBLE IMPORTANCE IN AUTOGENOUS DISINFECTION OF THE SKIN

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peroxides destructive to a number of organisms, especially the haemolytic streptococcus. Stevens reports also that lipoids of guinea pig skin take up oxygen, which is available in an active form and can be estimated by the oxidation of iron from the ferrous to the ferric form. This active oxygen is produced in the dark but its quantity is much increased by exposure of the skin or of the extracted lipoids to ultra violet light. Organisms, especially the haemolytic streptococcus, are killed, or their growth is inhibited by volatile peroxides given off by the irradiated lipoids, and both the active oxygen and the bactericidal power of the lipoids are annulled by the reducing action of cystein. No experiments were carried out with human skin and its fats, but it is not unlikely that these fats and those of sebum and sweat may produce similar peroxides. Stock and Francis (1940) inquired whether the ability of unsaturated fatty acids to form peroxides (Holm, Greenbank, and Dreysher 1927) is related to the sterilizing power which these acids possess. They observed that 1 per cent H_2O_2 kills the influenza virus, whereas 0·1 per cent is inadequate—a finding which agrees with mine on subjecting the haemolytic streptococcus to H_2O_2. They failed to detect peroxides in their fatty acid solutions, as I failed to detect them using the benzidine reaction and the Kerr Kreis test (Bolton, 1928) either in fatty-acid solutions or in suspensions of hair fat. Moreover boiling these suspensions did not impair their activity which therefore could hardly have been due to volatile peroxides. In any case, the concentration of peroxide lethal to virus and streptococcus could not arise from the amounts of fatty acid sufficient to kill these organisms (23–65 milligrams per cent).

I confirmed the inhibition by cystein of the streptococcicidal power of fats on ether extracts of skin, hair, etc., and on one or two fatty acids, and in a few experiments I noted that exposure to air with or without ultra violet light irradiation, increases or restores the disinfectant properties of cerumen or cystein inhibited hair fat, but, as these substances could not be shown to form peroxides and as the activity of the saturated stearic acid was more strongly suppressed than that of any other acid tested, I cannot conclude that cystein inhibits solely by reducing peroxides. Again I showed that blood, an oxidizing agent, is more efficient than is cystein in diminishing the streptococcicidal power of fatty acids whilst Bayliss (1936) has noted the diminution by blood and Noguchi (1907), Lamar (1911), and Walker (1924) the diminution by serum of the disinfectant property of soaps.

According to du Noüy (1922) the surface tension of aqueous solutions of serum, egg albumin, gelatin, etc. lowered by the addition of oleates, spontaneously returns to normal—a recovery which he attributes to the adsorption of the oleate upon the substrate molecules. Possibly cystein, like blood or serum, inhibits the bactericidal power of lipoids by interference with their power to lower surface tension, though cystein may sometimes act by reducing peroxides.

Cornbleet (1933b) as well as Bryan and Mallman (1933) recorded an increase in the sterilizing power of the skin after exposure to the sun or to ultra violet light. Schneider (1937) too observed that ultra violet or sunlight irradiation of the human skin induced a temporary heightening of its acidity, which may explain the increased sterilizing power of irradiated skin.

In short, of possible bactericidal factors operating on the skin surface—other than desquamation, desiccation, Arnold's physico-chemical mechanism, acidity

and fatty acids and soaps—peroxides and light, especially ultra violet, may be important. Other factors, such as lysozyme, menotoxin, and enzymes, with the possible exception of Trank's lipase, are of purely academic interest.

THE BACTERIA FOUND ON THE SKIN AND THE METHODS USED FOR RECOVERING THEM

Meleney (1927) remarked "The body surface is covered with countless pathogenic and non-pathogenic organisms, which penetrate for a variable distance into the cracks and crevices of the skin, and into the openings of the hair follicles and sweat glands." It is to Price (1938) that we owe the differentiation of skin bacteria into two groups, the "transients" and the "residents". The transients are acquired mainly by contact and vary greatly in both number and kind. They may be abundant on exposed skin, especially under the nails and in the skin folds, but are relatively scarce on clean protected skin. The "residents" form a comparatively stable group. Forces increasing their number (such as growth) and decreasing it (such as washing or desquamation) tend to reach an equilibrium. Protected skin has, as a rule, a somewhat larger resident flora than has unprotected skin. After reduction in number their re-establishment proceeds at a rate represented by a sigmoid curve, similar to that of bacterial growth in cultures. Hands and arms, thoroughly "de-germed" by scrubbing with soap and water, may not recover their full complement of "residents" for a week or more. Beneath clothing, the time required for regeneration of the normal flora is shorter (within sterile rubber gloves very much shorter) and eventually the flora may far exceed the usual number. The "transients" cling with dirt to the fatty coating of the skin, whence they are removed easily by washing. They comprise the bulk of the pathogens falling upon the skin. The "residents" include few pathogens, but are firmly adsorbed in some way to the skin surface or are embedded in its crevices. Price states that they are not recoverable from sweat or sebaceous glands or from hairs. A "transient" may, by frequent re-inoculation, become inured to conditions originally adverse and establish itself as a "resident", thus making a carrier of its host.

Vertaler (1940) asserted that the "residents" (*Hafthelme*) consist mainly of non-mannite-fermenting white staphylococci, presumably *Staph. epidermidis*, of various diphtheroids, and of *Sarcinae*. Though he agreed with Price in finding the sweat sterile, he disagreed in finding bacteria along the hair shafts. About 30 per cent of his subjects carried *Staph. aureus* on their hands and arms, and carriers were more frequent amongst those continuously exposed to infection or already suffering from a staphylococcal lesion. In most of the carriers the organism was present as a "transient", but in 13 per cent of them it had become resident. Widely divergent estimates of the *Staph. aureus* carrier rate have been published. Smith (1941), for example, puts it at only 5 per cent, Gillespie, Devenish, and Cowan (1939) at 20 per cent.

Colebrook (1941) included some aerobic spore-bearers and haemolytic streptococci among the "residents", and mentioned *Str. pyogenes*, *Staph. aureus* and *Coryn. diphtheriae* as frequent "transients". Washing with soap and water readily removes "transients" such as *Str. pyogenes* (Colebrook and Maxted, 1933), but only reduces the "residents".

The distinction between transients and residents was not upheld by Pillsbury (1942) who found that each successive washing of a skin area recovered the various bacterial species in similar proportions. This is the expected finding, if he was *dealing with a flora almost entirely* resident a possibility supported by his failure to recover any streptococci

According to Lovell (1945) bacteria can be found in the sebaceous glands and hair follicles, as well as on the surface and in the fissures of the skin. He suggests that the rapid reappearance of bacteria on skin rendered nearly sterile and covered with a rubber glove may be due to the increase of sweat, which raises the surface tension of the skin and draws up organisms from crypts, follicles, and glands. But, surely sweat with its content of electrolytes and short-chain fatty acids would lower rather than raise the surface tension? In areas supplied with sebaceous glands the continuous excretion of sebum must tend to restore surface bacteria by carrying them up from the glands and hair follicles.

A great variety of methods has been used for recovering bacteria from the skin (Viertaler 1940 Colebrook, 1941) These range from simply dipping the fingers or hands in nutrient broth or molten agar rubbing the skin with pledgets of moist cotton wool or scrubbing it with a brush into water to scraping it with glass strips, sharp spoons, or knives, or even to removing portions, grinding them up in a mortar and then culturing them.

Arnold and his colleagues (1930) Cornbleet and Montgomery (1931), Norton and Novy (1931 1932) Bryan and Mallman (1933) and Colebrook (1930, 1941) used a swabbing technique. Cornbleet (1933a) introduced saline into a glass cylinder pressed on to the skin, which was washed by gentle agitation of the fluid with a glass rod Marchionini and Schmidt (1938), in their later work, and I employed a similar method (Burtenshaw 1938 1942) but I have usually scraped the skin under the fluid with a glass slide. Price (1938) scrubbed the hands and arms with soap into successive basins of water Viertaler (1940), after allowing the hand to sweat inside a rubber glove, washed off the sweat in the glove and on the surface of the hand into molten agar

Clearly the method chosen will depend upon the problem to be solved If the aim is to estimate the total number of organisms, transients and residents in or on the skin then a drastic method such as Price s, will best serve but, if the aim is to discover the rate of disappearance of applied organisms, presumably transients from the skin surface, the chief requirement of the method selected is that it shall remove a fairly constant proportion of the superficial flora. In my own trials I concluded that swabbing failed to meet this requirement which was adequately met by the more exactly reproducible technique of the slide-and-cylinder method

PROBLEMS STILL UNSOLVED

Much research is needed to remove the discrepancies existing between the results of different workers and depending upon the many variables involved.

For example, the skins of different subjects do not show similar self-disinfective power I encountered one subject whose skin had no effect on a streptococcus readily killed by my own skin (Burtenshaw 1942) Hill and White (1933) found

that in a proportion of their volunteers, varying with the test organism used, the finger-tips failed to inhibit bacterial growth. Karns and Arnold (1931) record variations of disinfectant power during the menstrual cycle. (See also the work of Fisher and Blank, p. 175.)

Also different techniques yield contradictory results. My own fingers, tested by Hill and White's technique, had no inhibitory effect on a strain of *Str pyogenes* easily killed by saline or ether extracts of my palmar skin. Schiemann and Landon (1919), Arnold and his co-workers, Cornbleet, Colebrook, and others have reported the rapid disappearance of *Staph. aureus* and *Bact coli* from the skin. Singer and Arnold (1929) actually found that the coli-typhoid group of organisms disappeared from the skin more rapidly than did any others tested. Yet using my cylinder technique (1938) I could not confirm this action of living skin on *Staph. aureus* and, though ether extracts of skin were harmful to one or two strains of *Staph. aureus*, they had no effect on *Bact coli*. Of course, it must be remembered that ether extracts exclude the presence of any water-soluble bactericides.

Again different strains of any one organism, or even different cultures of the same strain, may behave differently under similar experimental procedures. Thus I found that hair extracts were lethal to some, but not to all, subcultures of a strain of *Staph. aureus* and to one, but not to another strain of *Staph. epidermidis albus*. Different strains of the influenza virus also evince different susceptibilities (see p. 162). This alteration of resistance of any one strain, or the different resistance of apparently similar strains, is illustrated in the work of Price and Viertaler discussed on p. 177. In order to co-ordinate and explain these discordant observations, a great number of skins must be examined by a standard technique with the employment of numerous species of micro-organisms and of several strains of any one species. Then correlation should be attempted between disinfectant power and such factors as *p*H, diet, drugs, metabolic disturbances, and fatty-acid content of different areas of the skin and of the skin of different subjects. Already Marchionini, Schmidt, and Kiefer (1938) have demonstrated that acid skin areas harbour less organisms than do alkaline skin areas. Cornbleet (1933a) has discussed the influence of diet and drugs on the bactericidal power of the skin. Arnold and Bart (1934) have observed increased autogenous disinfection on a ketogenic diet, which presumably increases the acidity of the skin. On the other hand Montgomery (1931) reported that the skin of diabetics has about half the disinfectant power of normal skin. Probably in diabetics the sterilizing action of increased skin acidity is more than counter-balanced by the nutritive value of glucose excreted in the sweat. Flandin and van der Elst (1942a) have found that the acidity of the skin falls on a vegetarian diet and rises on a normal meat diet.

Another problem is presented by the observations of Singer and Arnold (1929), Arnold *et al* (1930), and Arnold and Bart (1934), which seem to impugn the importance of fatty acids as skin disinfectants, since these workers stated that cleansing the skin with fat solvents increased, or at least did not impair its power to destroy *Staph. aureus* and *Bact coli*. On the other hand, some experiments of mine (Burtenshaw 1942) indicated that *Str pyogenes* disappeared more quickly from a normal than from an ether-cleansed area of the palm. Admittedly Arnold's experiments are supported by the clinically attested occurrence on

seborrhoeic skins of such infections as acne vulgaris, which is occasionally treated with success by removing the fats as completely as possible with hot water and soap. Possibly the growth of the acne bacillus is favoured by the lower acidity of seborrhoeic skin (Marchionini Marz, and Huss, 1938) more than it is hindered by the fatty acids and soaps, which are diluted with other lipoids and may indeed be inhibited by the cholesterol and its esters (Eggerth, 1927 Kodicek and Worden, 1945) Thus the occasional success of treatment with hot water and soap may well depend upon removal of a layer of inactive fat and the substitution of a film of active soap

Then there is divergence of opinion about the clinical efficiency of ordinary washing soap as a skin disinfectant There is no doubt that soaps kill *in vitro* a number of common bacteria and fungi, but micro-organisms vary greatly in their sensitiveness to individual soaps. *Staph aureus* for example, is most sensitive to laurate, abietate, and linoleate (p 174) which are absent in washing soap but *Bact coli* which is fairly sensitive to palmitate, and *Str pyogenes* which is very sensitive to oleate, should succumb to washing soap Colebrook (1941) believes that washing soap is germicidal to transients but Pillsbury and his co-workers (1942) and Price (1938) hold that the detergent action of soap and the scrubbing remove organisms from the skin but do not kill them

Another difficulty arises from the claim of Hermann and Fürst (1929) that various skin infections could be cured by sweat baths, although the sweat might become alkaline, and that concentrated sweat furnished even at pH 3·0, an excellent culture medium for staphylococci and yeasts, the growth of which was inhibited on the skin at pH 7·0 Usher (1928) grew various organisms in sweat containing media which were faintly acid also Cornbleet (1933b) asserted that staphylococci grew excellently in sweat at pH 8·0–3·0, but that, if this sweat containing the organisms was placed on the skin, they disappeared in a few minutes. A possible explanation of Hermann and Fürst's first finding is that soap, rather than fatty acids, was the disinfectant agent in the sweat and sebum, which would become continually more concentrated through evaporation also of their second finding that staphylococci (but not yeasts) are relatively insensitive to the short chain fatty acids, which preponderate in sweat, and that staphylococci and yeasts succumbed on the skin because they were there subjected to far more highly concentrated short-chain and long-chain fatty acids from sweat and sebum clinging to the surface.

These explanations might serve also for Usher's and Cornbleet's observations, though it is difficult to understand how any of the usual organisms could thrive at pH 3·0 as in the experiments of Hermann and Fürst and of Cornbleet.

Advances in therapy may be expected from studies of the local and general skin acidity and of any change in the constitution of the fat mantle in a number of infective, and possibly non-infective, skin diseases. Marchionini (1938) and Marchionini and Schmidt (1939) have found reduced acidity of skin in and around chronically infected or diseased areas, and this finding is confirmed by Bernstein and Hermann (1942) who point out that mycoses tend to localize in areas relatively alkaline, such as the interdigital clefts and skin folds. Williams and Sullivan (1944) state that the more acute an inflammatory lesion the lower are the Eh

and the higher the pH of the neighbouring and overlying skin whilst Flandin and van der Elst (1942b) claim that the skin bordering on a chronic lesion registers a subnormal Eh. (Eh is the millivoltage measured on the skin surface, and is inversely proportional to the pH. Flandin and van der Elst prefer to record their results in terms of Eh, which under the complex conditions prevailing on the skin is not always a simple function of pH.)

All these observations suggest that application to the skin of fatty acids and soaps, selected for their efficiency *in vitro* against the micro-organisms concerned, might well help in the treatment of infective lesions. The effectiveness of sweat baths (Hermann and Fürst, 1929 Marchionini, 1934) probably depends upon increased concentration of soaps and acids on the skin surface. Already synthetic soaps such as Dreft, which contains sodium lauryl sulphate (Bayliss, 1937), and Cub, which is cetyltrimethylammonium bromide (Williams *et al.*, 1943) have been introduced with success. Healing might also be helped by diets and drugs designed to increase the acidity of the skin.

Further attempts should be made to discover whether or not a mechanism of autogenous disinfection, similar to that described by Stevens (p. 176) in guinea-pig skin, also operates in that of other animals, including man. If such a mechanism exists, it may be disordered in infective skin diseases, and a full understanding of it would enable corrective measures to be devised and put into practice.

Finally further research on the enzymes of the skin might yield a golden harvest. If the existence of Tzank's lipase (*see* p. 175) should be corroborated and it were proved to be specific for the lipoids of the tubercle and leprosy bacilli, therapeutic fields would be influenced far beyond the domain of dermatology

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not produce trauma of the tissues, nevertheless, the maddening irritation set up by its presence on the rectal and anal mucosa is such as to result in the host inflicting on himself the severe excoriations familiar to all who are called upon to treat the infestation. Sometimes the mechanical trauma produced by the parasite is in itself considerable, and results in an extensive wound in the cuticle thus in the tropics, myiases caused by *Dermatobia hominis* may result in the invasion of the subcutaneous tissues by a number of larvae, each of which is more than one inch in length. Such an invasion is obviously serious as well as being very painful. Usually however the most serious results of myiasis are those which follow the invasion by bacteria of the wound made by the parasite, and the term cutaneous myiasis generally conjures up a picture of a septic ulcer, for the severity of which bacteria are more responsible than the diptera.

This picture of a mechanical injury followed by a secondary infection, is often further complicated as a result of the injection by the parasite of substances inimical to the host. Since these substances are usually injected by the parasite at the time when it first makes contact with the skin, they are often the particular concern of the dermatologist. The injected substance is usually derived from the salivary glands of the parasite, and its employment forms a necessary part of the creature's life-cycle, either as a means of facilitating its penetration into the tissues of its host, or as a means of allowing it to digest the food obtained from the host. That this digestive fluid may have a deleterious effect on the host is, so to speak, no concern of the parasite, to whose obvious advantage it is that the host should as far as possible remain in good health. The injection of a digestive fluid necessary to the development of the parasite, and which is common to most parasites, must not be confused with the injection of a poison used as a means of protection or aggression and playing no essential part in the life-cycle of the parasite. Many of the *Arthropoda* make use of such protective poisons, which may be injected by means of a sting in the case of the scorpions, bees, and wasps, by the claws or mandibles in the case of the centipedes and spiders, and from various regions in the case of the vesicant beetles. Much work remains to be done on the nature of these substances, but in general it can be stated that the digestive salivary secretions contain such substances as enzymes, red cell agglutinins, and haemolysins, whereas the poison injected by wasps and bees, etc is akin to snake venom.

The reaction of the human host to these two types of substances varies somewhat with the individual, and usually greatly with the number of previous injections to which he has been exposed. It is known that sensitization, sometimes followed by immunity or tolerance, may be acquired to both salivary secretions and poisonous stings. Man's reaction to the latter will be discussed later but since the injection of salivary secretion is common to almost all parasites which pierce the skin, and since it plays an important part in the transmission of certain diseases, as well as causing skin lesions, its effects may be discussed appropriately at this point

As already stated, the injection of digestive substances by the parasite is part of its normal cycle, and does not necessarily injure the host. Nevertheless, it frequently does so, and in consequence certain parasites, such as fleas, lice, mosquitoes, bed-bugs, and mites, to mention only a few widely distributed examples,

CHAPTER 9

PARASITOLOGY IN RELATION TO DERMATOLOGY

R. M GORDON

INTRODUCTION

THE term human or medical parasitology is usually understood to apply to a study of those living organisms which for the purpose of procuring their food take up their abode temporarily or permanently on or within the body of man. It is generally recognized however that the scope of the term medical parasitology is expanded to include certain biting, stinging, or vesicant creatures, which do not fall within the meaning of the phrase, taking up their abode to obtain food. On the other hand most, although not all authorities use the term in a restricted sense, which does not include spirochaetes, bacteria, or fungi.

If we accept these expansions and restrictions and confine our study to dermatology it will be necessary to consider certain members of four phyla or tribes in the living world, the *Protozoa* the *Nemathelminthes*, the *Platyhelminthes* and the *Arthropoda* certain members of which, at some stage of their curious and complicated life-cycle cause pathogenic changes in the skin of man.

It is usually taken for granted that the reaction between the parasite and the host is always to the disadvantage of the latter but this is not necessarily so. Among the *Protozoa* infection with the malaria parasite is frequently used as a treatment for syphilis amongst the worm like parasites, leeches are still employed for blood letting among the *Arthropoda*, bee stings, or the injection of the venom of the bee, are not infrequently prescribed in rheumatism while application of the larvae of certain flies has been recommended for the treatment of osteomyelitis and cleaning up septic wounds of the skin. This utilization of fly-larvae as a therapeutic measure in dermatology has now been largely abandoned, since the aesthetic disgust produced by this rather repulsive form of therapy probably outweighs any benefits derived from its use, whilst the difficulty of ensuring that the larvae are free from bacteria has been known to result in tetanus (Mackie *et al.* 1945). Although the use of larvae has been largely discontinued the active substance produced by them allantoin is sometimes prescribed (Kaplan 1937) But the efficiency of this traditional remedy has yet to be placed on a firm basis (*Kaplan, Annotation* 1942)

In general however the beneficial effects produced by the parasite in the human host are virtually negligible and we need only concern ourselves with those parasites producing pathogenic effects.

These pathogenic effects, so far as the skin is concerned may be produced in a variety of ways. Occasionally the parasite does not directly injure its host thus, so far as is known the threadworm does not secrete a poison or toxin and does

transmitted to him in the saliva of the biting insect will ultimately result in lesions which are the direct concern of the dermatologist. Thus, filariasis, conveyed by the mosquito may eventually cause calabar swellings or elephantiasis, according to the species of helminth larva injected with the salivary secretion the trypanosome conveyed by the tsetse may result in the rash of sleeping sickness, the rickettsias transmitted by various arthropods in rashes associated with different forms of typhus, whilst the *Leishmania* injected by the sand-fly may give rise to ulcers of the skin. The relationship of such parasites to skin lesions will be discussed later but it is appropriate at this point to draw attention to the fact that immunity or tolerance on the part of the vertebrate host to the salivary secretion of the insect vector in no wise implies a similar tolerance or immunity to the parasite transmitted in the saliva

Apart from the injuries already considered, it is sometimes stated that parasites may directly or indirectly produce skin lesions by the production of toxins It is true that certain parasites, notably the helminths, probably produce toxins, but our knowledge of these is very slight, and the term is frequently confused with the development of sensitization in the host to some protein constituent of the parasite. Thus, many workers have in the past described a toxin produced by *Ascaris lumbricoides*. More recent work, however would appear to show that the reaction to the so-called toxin is an allergic phenomenon, and that, in general, only those persons previously sensitized to *Ascaris* and subsequently brought in contact with the worm will develop urticaria.

F nally reference must be made to the association between certain parasites and the development of neoplasms of the skin and mucous membranes, the latter being sometimes of a malignant nature. Amongst the lower animals the association between certain helminths and the development of malignant growths is well recognized (Chandler 1944) whilst in man the rectal ulceration and prolapse produced by *Schistosoma mansoni* infection is not uncommonly the site of a primary carcinoma.

Against the arious ill effects produced by parasites which injure the skin, medical science has developed a variety of protections and treatments. On the whole we can record but few advances in treatment, although there are some outstanding exceptions which may more conveniently be described when individual parasites are being considered. On the other hand, the advances in protection ha e been great, although in the main the credit for their discovery goes to the biologist rather than to the physician. In this connexion it must not be forgotten that the physician shares with the biologist the responsibility for the control of the paras te, and that this control involves a study of the parasite, not only in the human host, but before it has reached him and, sometimes, after it has left him.

We have seen that medical parasitology is usually considered to include the protozoa, the helminths, and the arthropods, in addition to various vesicant creatures, and that a large number of members of each of these three great phyla are capable of and often do produce lesions in the skin of man. It is probably simplest to consider each of these phyla in turn, and to make reference to those members in each family which are of special importance in dermatology The following account of these creatures is written, not so much with the object of

have become notorious as causes of dermatitis. The host's reactions to the substances produced by these creatures may be immediate, but it is more often delayed for several minutes and sometimes for several hours. This reaction, whether immediate or delayed probably differs considerably in different individuals, and almost invariably alters in its intensity in persons exposed to the same species of parasite over a prolonged period This alteration in the host's reaction has led to the quite erroneous belief that, in the tropics, the indigenous native is not bitten by mosquitoes, and that although the long-resident European is bitten, he is not bitten to the same extent as the newcomer Practical experiments have shown that the mosquito takes no notice of this belief and indifferently bites all three, but whereas the newcomer reacts mildly at first and later more vigorously to each injection of salivary secretion the older resident notices it but little and the native not at all (Gordon, 1922) How this relative immunity is acquired is not clearly understood, although it is known that its completeness and its duration vary considerably in different individuals, and that the immunity tends to be of a local nature, so that those areas of skin most subjected to bites obtain their immunity before those which are less exposed (Blacklock and Gordon 1927). It appears certain however that the majority of persons, prior to obtaining their immunity to reaction, become sensitized to the salivary secretion of the biting insect. This period of sensitization has been described by Theodor (1935) in the case of *Phlebotomus* (the sand fly) which causes the skin eruption known as harara in Palestine, whilst a similar sensitization has been described by Mellanby (1943) as occurring in scabies. Our knowledge of the nature of the substance to which these reactions are developed is very scanty but the antigen is clearly of a highly specific nature, for the same individual may be completely tolerant or immune to the bite of one species of mosquito while markedly sensitive to that of another species (Mellanby 1946) This specificity suggests that it is highly improbable that any form of treatment by antigens can be successfully employed to render a patient tolerant or immune to insect bites in general On the other hand the desensitization of persons susceptible to the bites of certain insects, in this case fleas, has apparently met with some success (*see* p 207)

This acquired tolerance or partial immunity on the part of the human host to the secretions of the parasite has been well recognized for a considerable period, but our conception of immunity to the parasite itself that is to say inhibition of growth and subsequent death of the parasite in the tissues of the host, as distinct from mere tolerance of its presence has within recent times undergone considerable expansion so that it now extends beyond the viruses and bacteria, to include certain of the *Protozoa* and quite a number of species of arthropods, although complete immunity to helminth parasites has never been proved (Taliaferro, 1930). The discovery that the human host commonly develops antibodies to such a diversity of parasites has led to the development of various diagnostic procedures, including complement fixation precipitin and skin reaction tests being applied not only for the recognition of infections due to protozoa but also for those due to metazoan parasites of such widely different types as tapeworms, flukes, round worms, insects, and mites.

It must not be forgotten that many blood sucking arthropods are themselves victims of parasites whose ultimate host is man and that certain of the diseases

Ancylostoma braziliensis, normally a parasite of cats and dogs, enters a human host, it wanders aimlessly in the more superficial layers of the skin, thereby causing the curious condition referred to as larva migrans. The term larva migrans is not confined to helminths, and has been applied to a variety of non-specific parasites, including the larvae of certain flies, whose normal habitat is the skin or mucous membrane of horses or cattle.

The majority of the human parasitic nematodes pass their entire adult existence in the gut or more rarely in the internal organs. In some species, however the adults inhabit the subcutaneous regions while others appear in this region or in the skin during some part of their wanderings. Thus *Onchocerca volvulus* causes subcutaneous tumours in man in Africa and South America, while the larvae produced by the female are confined to the deeper layers of the skin and, contrary to the habits of most of the microfilariae, do not appear in the circulation. The presence of the adult worm and of the larvae of *O. volvulus* in these dermal sites results in certain well-marked skin changes (Hettel, 1944; Goldman and Ortiz, 1946). The adults of *Wuchereria bancrofti* occur in the lymphatic system, and the larvae in the blood, while the adult *Loa loa*, instead of remaining in one locality, moves about in the connective tissue, and appears beneath the skin in various parts of the body, its predilection for the eye having been known since early times. The presence of the adult *W. bancrofti* and *L. loa* leads to curious swellings known as calabar swellings. The significance of these swellings is not fully understood, but it is generally agreed that they are allergic phenomena, and that their location is not necessarily associated with the site of the worm.

Dracunculus medinensis, the guinea-worm, is transmitted to man when the latter swallows the infected intermediate host, *Cyclops*, but the adult female only reaches the skin during the last stages of her development. At this time she causes an ulceration of the skin, usually in the region of the foot. If this ulcer comes in contact with water the female protrudes her body and discharges her progeny.

The ubiquitous *Enterobius vermicularis* inhabits the colon, but oviposition is performed on the peri-anal skin, and the wanderings of the female worms in this region lead to persistent itching and subsequent excoriations of the skin and mucous membrane.

Both *Ascaris* and *Trichinella* infections have been associated with skin eruptions, such as intense pruritus and various rashes. The cause of these manifestations has been ascribed to toxins produced by the parent and larval or parent or larval stages of the worms, whilst sensitization to *Ascaris* is not uncommon amongst workers in biological laboratories who, although not themselves infected, are brought in contact with these helminths (Craig and Faust, 1940).

In infected persons cure seems dependent upon killing and, where possible, expelling the worms. In this connexion it should be remembered that dead helminths, particularly *Ascaris*, are liable to produce toxic manifestations when left *in situ*. For the treatment of larva migrans Loewenthal (1939) has recommended spraying the skin immediately in front of the advancing larva with ethyl chloride. Vassallo (1939) claims good results following 30 seconds exposure to x-ray irradiation.

supplying a description of the parasite, its life-cycle, and the lesions it produces—this would be far too ambitious a project—but rather to suggest to the dermatologist the advisability of remembering that outside the realms of bacteriology and mycology there exists a multitude of parasites which directly or indirectly affect the skin It is true that many of these parasitic infections of the skin, which we are about to describe, are acquired only in the tropics. Under modern conditions of transport when not more than three days separate any two towns of the earth's surface, this no longer appears to be a valid reason for omitting them from consideration

For reasons of space no attempt has been made to supply descriptions which would allow of the identification of the various species mentioned, all of which are figured in modern text-books on parasitology such as Belding's (1942). Illustrations of certain of the lesions caused by parasites are somewhat widely scattered in various standard works on dermatology whilst a very complete set of photographs has been gathered together by Nékám (1938)

PHYLUM PROTOZOA

At least eight genera of protozoa contain species which are pathogenic to the human host but if we exclude the comparatively rare skin lesions due to *Entamoeba histolytica* the incidental rash due to *Trypanosoma gambiense* and if as is done by most authorities we omit the spirochaetes from the protozoa only one genus, *Leishmania* is definitely associated with skin disease.

The invasion of the skin and subcutaneous tissues by *L. tropica* and of the buccal and nasopharyngeal mucous membrane by *L. braziliensis* is, of course, well recognized on the other hand it was formerly believed that *L. donovani*, the cause of kala-azar was confined to the internal organs. More recent work, however has shown that in certain cases there not uncommonly exists a condition known as post kala azar dermal leishmaniasis in which the skin although not ulcerated is extensively invaded by the *Leishmania* parasite, and that such cases, together with a canine reservoir consisting of dogs with similarly infected skins, form a focus of the disease, from which the sand fly acquires the infection which it transmits

PHYLUM NEMATHELMINTHES

Nemathelminthes or roundworms have simple or complex life-cycles, both within and without the human host, and certain of them during their invasion of the host and during their subsequent wanderings, may produce a variety of skin lesions. Penetration of the host's skin by the larval stage of the worm is common to many species notably the ancylostomes or hookworms. Ancylostomiasis, although mainly a disease of the tropics, was at one time common amongst the Cornish tin-miners who called the skin reaction caused by the penetration of the larvae, bunches the more significant term, ground itch being applied to the same condition in the tropics. In cases where the invading larva penetrates the skin of its normal host it works its way into the blood-stream and continues its development in the internal organs If however the larva finds too late that it has penetrated the skin of an unsuitable host as happens, for example, when

PHYLUM ARTHROPODA

Members of this phylum, which includes insects, affect the health and well-being of mankind to an extent not generally recognized, and it is true to state that the colonization of empires and the outcome and duration of wars have often been determined by their activities. For the most part, these far-reaching results have been achieved by arthropods in their role of transmitters of virus, bacterial, protozoological, and helminthological infections. Certain of the diseases thus transmitted may directly or indirectly result in lesions of the skin, and some of the protozoological and helminthological aspects of this subject have already been considered. It is, however with the more obvious, although much less important, role of arthropods as temporary or permanent ecto-parasites that the dermatologist is mainly concerned.

CLASS ARACHNIDA—ORDER ACARINA

Family Trombidiidae

This family contains the genus *Trombicula*, the larval stages of which attack man and animals in almost all parts of the world. In Great Britain the common species is *T. autumnalis*, which is usually referred to as the harvest mite or orange tawny. The eight-legged adult and nymphal stages are free-living forms which do not suck blood, a statement which also applies to all members of the genus whose life-cycle is known, but the six-legged larvae readily attack any warm blooded animal including man. These larvae are minute creatures (about 1 millimetre), which during the summer months, particularly towards the end of summer swarm with a furious activity over vegetation and soil, showing a particular preference for low-growing fruit trees and bushes. Once it finds its way on to the skin, the larva moves quickly to cover and owing to its small size and rapid movement, it is seldom noticed until it comes to rest, usually at some constriction in the clothing, such as the waist line. At this point it pierces the skin and by regurgitating the gut contents to and fro, it produces a curious feeding tube which passes into the corium and causes an area of hyaline degeneration in its passage through the *stratum corneum*. When seen *in situ* the larva appears as a minute red or orange speck on the centre of the skin area reacting to the bite. Normally the feeding mite remains attached to the skin for about 24–48 hours, at the end of which period it drops to the ground to complete its life-cycle. The reaction produced to the bite, however is usually delayed for several hours and is then sufficiently severe to induce the victim to scratch with a vigour and thoroughness which frequently results in the destruction, or at any rate the removal, of the source of irritation. These facts probably explain why only a very small proportion of the bites reveal the presence of the mite and, in consequence, the common failure to diagnose the condition.

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PHYLUM PLATYHELMINTHES

Class Trematoda

Various species of trematodes or flukes are parasites of man and, as in the case of the roundworms, the presence of the adult flukes may cause skin reactions ascribable either to allergic reactions due to the presence of the worms, or else to the production of toxins by the parasites, while Black (1945) has described a dermatitis caused by the presence of *Schistosoma haematobium* ova in the skin. In addition, those species which inhabit the veins of the gut, such as *S mansoni* and *S japonicum*, may cause prolapse of the rectum and anal or peri-anal lesions. Their most characteristic association with skin infections however is due to the penetration of the human skin by the larval stages of the trematodes, and since the skin-penetrating stage is usually that which follows the development of the parasite in an aquatic mollusc this stage of invasion is usually associated with water and the resultant dermatitis is commonly referred to as bather s rash or swimmer s itch Here again as in the case of the roundworm larvae, the penetration of the skin may be made by larvae which enter the skin of man as a specific host, or by larvae which have mistaken their victim. In the former case development proceeds to adult form whilst in the latter case the larvae perish in the skin the results, so far as the dermatologist is concerned being similar

The species of schistosomes or blood flukes which have man as their specific host are for the most part confined to the tropics. On the other hand, a very large number of mammals and birds in temperate as well as tropical climates are parasitized by blood flukes the larvae of which will pierce the skin of any warm-blooded animal and in consequence cases of swimmer s itch are widely distributed and have been reported from many temperate American and European countries, including Great Britain (Matheson, 1930 Taylor and Baylis, 1930). Children appear to be affected more frequently than adults, possibly because of their tendency to bathe in the shallow water where the cercariae, the larval forms of the schistosome most commonly occur A typical history is that after bathing, as the water evaporates from the skin a prickling sensation is experienced, followed by urticarial weals Usually several hours later an intense itching develops with oedema and the papules may become pustular

Class Cestoda

More than twenty species of tapeworms have been recorded from man, but only four of these are common parasites, and only three of them (all in their larval form) are likely to be associated with dermal lesions. *Taenia solium* and *T echinococcus* have a world wide distribution and their larval stages, which normally occur respectively in muscle and liver may be present as subcutaneous nodules. *Sparganum mansoni* the larval form of *Diphyllobothrium mansoni* is confined to the tropics, and is usually found encapsulated in the subcutaneous tissues, and not uncommonly in the conjunctiva (Baer 1945) Occasionally larval cestodes, normally parasitic in other animals, occur in or below the skin of man thus, *Coenurus* normally a parasite of cattle, has been found in the subcutaneous tissues of natives in various parts of the world Medicinal treatment undertaken to destroy the encysted larvae is usually unsatisfactory and when necessary removal by surgical means must be employed

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the mites whilst clothing which has been impregnated with dimethyl phthalate or benzyl benzoate renders the wearer virtually immune from attack. There appears to be no specific treatment for the local reaction produced by the bite, which although intensely irritating seldom persists for long periods, and does not usually suppurate. A different picture, of course, follows the invasion of the skin by a mite infected with *Rickettsia orientalis*, the cause of mite-borne endemic typhus in such instances the site of the infected bite is marked by the appearance of an eschar or chancre, presumably as a result of the local development of the rickettsias The voluminous literature concerning *Trombicula* and its control is well summarized by Farner and Katsampes (1944)

Family Dermanyssidae

Certain blood sucking mites belonging to the genera *Dermanyssus* and *Liponyssus* attack both birds and rodents, and in the absence of these normal hosts they will attack man the two species most frequently involved being *D gallinae* the so-called red fowl mite and *L bacoti* the rat mite. Both species have an almost world wide distribution and many cases of human dermatitis due to their bites have been recorded

These mites have habits somewhat similar to those of the bed-bug, and usually remain concealed in cracks and crevices during the daytime, whilst during darkness the larvae and the adults of both sexes sally forth to look for a blood meal. Like the bed bug, but unlike the harvest mite the *Dermanyssidae* feed to repletion in a few minutes and having fed retire to their shelters. These habits, combined with their small size and ability to travel long distances in search of food, have on occasions resulted in the unfounded diagnosis of maladie imaginaire or where the bites were eloquent testimony to the truth of the patient s complaint, their cause has been unjustly attributed to fleas or bed bugs, the injustice being rendered serious by the fact that the measures adopted against these latter insects are unlikely to get rid of the mites whose extermination or expulsion is best effected by tracing them to their source, which in the case of *D gallinae* is the fowl-run, and in the case of *L. bacoti* the breeding place of the black rat but it must not be forgotten that *D gallinae* will live and multiply not only in poultry houses, but also in the cages of birds such as canaries and parrots. If it proves impossible or inexpedient to remove the source of trouble, dusting the mites retreats with Gammexane powder generally proves effective.

Although *D gallinae* the poultry mite, is most frequently associated with human outbreaks, similar outbreaks have been traced to other species of mites inhabiting pigeon lofts or the nests of swallows near bedroom windows, while it is probable that rodent mites, other than *L. bacoti* are sometimes concerned in causing dermatitis (Hill and Gordon 1945)

Family Pediculoididae

One member of the family *Pediculoides ventricosis*, is notorious as causing a dermatitis associated with the handling of grain products or straw hence the name, grain shoveller s itch commonly applied to the condition. The association of *P ventricosis* with grain and straw is due to the fact that this mite normally feeds on the larvae of insects which live in such materials and it is only when these have

been consumed or have died off, that the mites, wandering in search of further food supplies, come in contact with man and give rise to an outbreak of dermatitis. These habits explain why such outbreaks only occur when the grain has been stored for some time and particularly if stored in a confined space, such as on board a ship. In these circumstances the mites may attack the inhabitants of the ship in large numbers and, later when the ship has reached port, the men who unload and store the cargo. These mites, when present in sufficient numbers, unquestionably produce a troublesome dermatitis, which is usually confined to such exposed areas as the neck, chest, and forearms, very severe or generalized reactions usually being traced to sensitization following previous exposure to the mites. Most authorities agree that the mites attach themselves only feebly to the skin, and are usually removed by a hot bath or shower followed by a change of clothing (Nixon, 1915). On the other hand, certain types of patients vigorously deny that the mite may be thus simply dispensed with the latter view is probably due to the fact that such patients are usually those whose work causes them to be constantly exposed to reinfection, but the fact that extra pay is attached to working dirty cargo should not be forgotten.

Family Tyroglyphidae

Unlike the mites previously described, the *Tyroglyphidae* have no power of piercing or penetrating the skin of man, although some species are said to conceal themselves under the superficial scales of the epidermis (Belding, 1942), nor is there any convincing evidence that they secrete any specific poisons or irritating substance. It seems probable, therefore that the various reactions, including dermatitis, which develop in certain individuals when brought in contact with tyroglyphid mites are in the nature of allergic phenomena, following sensitization to some protein present in the cuticle or excretions of the mites. This view was put forward, many years ago, by Hase (1929), who showed that it was not necessary for the mites to attach themselves to the skin, mere contact with infested food or other substances containing the powdered excrement, or the shrivelled corpses of the mites themselves, being sufficient to cause the dermatitis in a sensitized person. More recently Carter and D Abrera (1946), and Soysa and Jayawardena (1945) have both suggested that the presence of tyroglyphid mites in the lungs may result in sensitization associated with asthma and eosinophilia.

The dermatitis which sometimes follows the handling of certain mite-infested substances is generally given a name associated with the material and quite commonly a certain species of tyroglyphid mite is named as the cause. Thus, to quote only a few examples, baker's itch associated with flour infested with *Tyroglyphus farinae* vanillism ascribed to the presence of *T siro* on the pods handled by vanilla workers, and copra itch caused by *T longior* It would appear however that the various species of *Tyroglyphidae* held responsible for these differently named conditions are widely distributed and often occur as a mixed fauna on the same material. It is probable therefore, that the exact species is relatively unimportant and what determines the occurrence of the dermatitis is the presence of mites in vast numbers on material which is repeatedly brought into close contact with the workers. Treatment is by the usual local applications, and prevention by tracing the cause of the trouble to handling a particular substance, and then

ascertaining whether it is the substance or its mite population which is causing the skin reaction

Family Sarcoptidae

Two genera of burrowing mites, *Notoëdres* and *Sarcoptes* cause scabies in man. The former is a parasite mainly of rats and cats, and is of rare occurrence in man, but the mite *S scabiei* in the latter genus, is a common human parasite with a world wide distribution Many varieties of mites within the species are recognized, and although scabies is usually caused by *S scabiei* var *hominis* passing direct from man to man it is important to realize that numerous other varieties, each named after its normal vertebrate host, may be the cause of the trouble. Such occasional infections are not limited to *S scabiei* var *equi* the cause of cavalry man's itch but may be derived from almost any animal suffering from *Sarcoptes* infection, and brought into close contact with man These aberrant infections yield easily to treatment and cannot maintain themselves for long periods in the human host.

Until recently the life-cycle of *S scabiei* was a subject of considerable difference of opinion The recently published memoir of the Danish worker Heilesen (1946), however seems to leave little doubt that the life-cycle is essentially that originally described by Hebra (1868) and shown to be similar to that of *Notoëdres* by Gordon, Unsworth and Seaton (1943) Having hatched out from the eggs laid by the female, the majority of the larvae escape from the parent tunnel and wander on the skin but a proportion remain in the parent tunnels or in side pockets off the tunnels where they can continue their development, at least as far as the nymphal stages. Of those which reach the skin surface many perish without further development, whilst some burrow into the intact *stratum corneum* to construct their almost invisible moulting pockets. Once established in its minute pocket the larva makes no attempt to extend it, but feeds and grows within its narrow limits until it is ready to cast its skin and become a nymph. The resultant first nymph either remains in the larval pocket or leaves it to construct a similar pocket in another area. In either case it moults again within the pocket to become the second nymph which behaves similarly to the first either remaining in the pocket or leaving it to construct a duplicate refuge in which the final moult occurs, resulting in the production of the adult male or female. It follows from this account that any or all of the three moults undergone by the developing mite may occur in the original larval pocket This process of development from egg to adult life occupies some 17 days

Since the eggs laid by the female remain in the skin, transmission must occur through the active forms of the mite, and Gordon and Unsworth have shown that in *Notoëdres* infections the larvae are mainly responsible, but experimental evidence is lacking to show whether the same stage is responsible for transferring human infections. Although evidence is lacking regarding the stage and the life-cycle responsible, it is certain that infection usually passes as a result of direct contact between infected and uninfected persons and, although much more rarely by indirect transference on fomites In both forms the risk is dependent upon the closeness of contact. Human scabies is frequently spoken of as a venereal or more accurately as a family disease whilst it is generally agreed that the same rule holds good for indirect transfer underclothing being more dangerous than the

outer garments, and sheets more dangerous than blankets. The mite, at whatever stage, and however conveyed, may wander considerably before penetrating the skin, and when left to her own devices, she tunnels wherever the skin is soft and wrinkled, or folded at the joints. Our knowledge concerning the cause, construction, and contents of the burrows of the ovigerous females is in marked contrast to our ignorance concerning these points in the case of the so-called scabies rash. Mellanby (1944) holds that the individual papules and the itching associated with them are not caused by the burrowing of any stage of the mite, but are due to a tissue reaction, resulting from the sensitization of the human host to some protein constituent or product of the invading mite. Heilesen, on the other hand, although he confirms Mellanby's observation that itching is less severe in primary than in secondary infections, has failed to obtain any specific response to intradermal tests, and has shown that the vesicles often contain mite remains, and are probably the resting places of the immature forms.

The successful treatment and control of scabies is dependent upon a knowledge of the life-cycle and habits of the mite, together with the use of an efficient sarcopticide. As regards the destruction of mites on the person, all authors are agreed that the essential criterion for success is that every portion of the patient's skin, except the head and neck, must be covered with the sarcopticide. Further there is general agreement that the use of hot baths and soap prior to the application of the treatment, renders the latter more efficient. Inorganic sulphur is a highly efficient sarcopticide, but owing to its tendency to produce dermatitis when used too freely the drug has largely been replaced by organic sulphur preparations, such as dimethylthianthrene, tetraethylthiuram monosulphide (Tetmosol), and tetraethylthiuram disulphide, the latter according to Heilesen, being somewhat inferior to Tetmosol. These preparations should be rubbed into, not painted on to, the skin. As a lethal agent benzyl benzoate, when used in a 25 per cent emulsion, and painted on to the skin, is as effective, or more so, than the organic sulphurs already referred to. Although much debate has occurred regarding the number of treatments necessary, it is clear from the literature that whereas the authorities differ regarding the percentage of cases cured by one application, all are agreed that a higher proportion is cured by two applications. It follows, therefore, that a single treatment is a matter of expediency and the practitioner would be well advised to prescribe two applications and, when possible, to arrange for a four or five days' interval between applications, since larvae are less resistant than eggs. A somewhat similar situation holds regarding the necessity or otherwise of treating fomites, and since all are agreed that fomites occasionally carry infections, it is a doctor's duty to advise disinfestation, when this involves no excessive labour on the part of the individual or the State.

As regards prophylaxis, it is probably of but little value to advise avoidance of contact, whilst the experience derived from the war has shown that the impregnation of garments, which proved so successful against lice, is useless in preventing the acquirement of scabies. The use of soap, impregnated with five per cent Tetmosol, has so far yielded the best results (Gordon and Unsworth, 1944; Bartley *et al.*, 1945). The whole position regarding scabies and its control will be found admirably summarized in Heilesen's monograph (1946), although, owing to the war, certain recent publications were not available to this author.

SUPERFAMILY IXODOIDEA—FAMILIES IXODIDAE AND ARGASIDAE (TICKS)

All species of ticks are blood sucking ecto-parasites, the majority feeding on the lower animals including mammals, birds, and reptiles, but many species will attack man when deprived of their more normal hosts. The superfamily *Ixodoidea* is divided into two families, the *Ixodidae* or ixodid ticks, and the *Argasidae* or argasid ticks members of the former family possess a chitinous shield, or scutum and are generally referred to as hard ticks whereas species occurring in the latter family lack this character and are spoken of as soft ticks The argasid ticks, certain species of which transmit endemic relapsing fever to man, have habits somewhat similar to those of the bed bug, feeding at night and completing their meal in a few minutes whereas the ixodid ticks, which are vectors of various rickettsial diseases, remain attached to their host for several days. During this period of attachment the injection of the tick s salivary secretion produces certain well marked pathological changes in the skin of the host, which have been described by Hoeppli and Feng (1931 and 1933). In order to reduce these dermal reactions, and also to minimize the risk of transmission of disease (since ticks, unlike biting flies, tend to convey infection only during the late stages of feeding) it is advisable to remove the ticks with as little delay as possible While on the host the mouth parts are deeply imbedded in the skin and, since they are armed with backwardly directed spines, attempts at removal of the tick often result in the so-called head being left in the wound, where it continues to cause irritation and sometimes forms a nidus for secondary infection A pledget of cotton wool, soaked in chloroform or petrol if applied a few minutes previous to the attempt at removal will render extraction easier If the tick is imbedded in such sensitive areas as the scrotum or peri-anal region, vaseline or medicinal paraffin may be substituted

ORDER DIPTERA

Certain members of the order *Diptera* or two-winged flies, may deleteriously affect the health of man in a number of ways. Unquestionably it is as vectors of disease that they fulfil their most dangerous role, but the importance of this role has already been briefly discussed and in any case, it is only indirectly the concern of the dermatologist. In addition however the adult forms of flies which bite man in the sense of sucking his blood are in the habit of introducing into the human tissues secretions which result in skin reactions of varying severity whilst the larvae of certain species have adapted themselves to a parasitic existence in the skin and subcutaneous tissues

In Great Britain the following families within the order contain species which are persistent biters of man the *Culicidae* which contains the mosquitoes the *Ceratopogonidae* which includes all the blood-sucking midges in the genus *Culicoides* the *Tabanidae* or horse flies, and the *Muscidae* in which occurs the so-called stable-fly *Stomoxys calcitrans* In the tropics certain small black flies or buffalo flies which are rather larger than midges and belong to the family *Simuliidae* frequently attack both man and his domestic stock in vast numbers. In this country however although widely distributed and probably the commonest biting fly feeding upon

domestic animals, they rarely attack man. Finally there are certain degenerate diptera belonging to the family *Hippoboscidae* which, although not parasitic on man, will nevertheless bite him if brought into direct contact for example, the winged *H equinae* and the wingless *Melophagus ovinus*, which normally feed respectively upon horses and upon sheep.

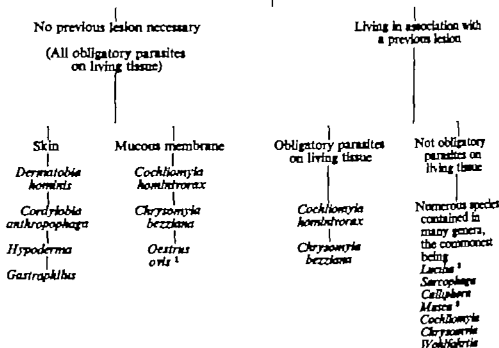
In Great Britain the number of species of two-winged flies which habitually or occasionally bite man is probably less than 50, all of which species occur in the five families just referred to In the tropics these five families are all represented and contain many hundreds of biting species not occurring in Great Britain. In addition there is another family the *Psychodidae* which contains a genus *Phlebotomus*, not present in Great Britain, some members of which are persistent and troublesome biters of man, not only in the tropics, but also in the subtropics and in Southern Europe. The severe dermatitis which may result from the bites of these insects, commonly referred to as sand-flies, has been described by various writers (Theodor 1935 Dubarry and Girand-Costa, 1941) As in other forms of dermatitis caused by insect bites, the severity of the reaction produced by *Phlebotomus* is probably dependent upon previous sensitization.

The salivary secretions of these different species of blood-sucking diptera probably vary considerably and although we have some little knowledge of the anti-coagulants, haemolysins and agglutinins present in a few of them, little appears to be known regarding the nature of the reaction which follows upon their introduction into the skin. The advice given for the treatment of insect bites is, therefore, usually empirical and mainly directed to the prevention of secondary infection.

In addition to the injury produced by the adult diptera when feeding upon the skin the larvae of certain species invade the tissues of man, the resultant condition being referred to as myiasis.

External myiasis or dermal myiasis, the term being used to include invasion of the mucous membranes and conjunctivae, has attracted considerable attention and the large number of species recorded has led to considerable and, possibly unnecessary confusion since just as in the case of the bacteria, any fly larva which can develop on dead meat is also capable of development on dead or moribund tissues, such as occur in septic wounds or malignant growths. Such chance invaders can scarcely be regarded as causal organisms and, if they are omitted from consideration, there remains only a very limited number of species of diptera whose larvae can be considered as causing dermal myiasis in man These true myiasis-producing species, although few in number are distributed amongst the following seven genera *Hypoderma*, *Gastrophilus*, *Oestrus* *Cochliomyia*, *Chrysomyia* *Cordylobia*, and *Dermatobia* The first three of these genera, all of which contain species occurring in Great Britain are mainly parasites of domestic stock and, although cases of human infestation are reported from time to time, they must be regarded as rare and accidental parasites of man, in whom they only survive for a limited period. Each of the four last-named genera contains only one, or at most two, species the larvae of which are true parasites of man. Flies belonging to these remaining four genera are a common cause of serious forms of myiasis in many parts of the world but they have not been recorded in Europe.

EXTERNAL MYIASIS IN MAN



[1] A rare accidental parasite of man.
Occurring in Great Britain.

The treatment of the various forms of myiasis produced by these different species essentially consists in removing the parasite and treating the lesions caused by its presence In the case of open wounds the removal is a simple matter but when the larva is deeply embedded beneath the skin as in the case of *Dermatobia* and *Cordylobia* infections, or where the larva has penetrated into the turbinal mucous membrane or even into the frontal sinuses, as in certain cases of *Cochliomyia* and *Chrysomyia* infections their removal may call for surgical interference. In the case of invasion by parasites of small size, as occurs at the time of invasion, or where growth of the parasites is stunted, as is usual in larva migrans types of infection it is probably quite satisfactory to kill the parasites *in situ*, without paying particular heed to their removal. On the other hand, the destruction by means of chloroform or other insecticidal agents, of well-developed, large parasites, deeply situated in the tissues, without ensuring their subsequent removal may be fraught with serious consequences Under these conditions an attempt should be made to remove the larvae and whether or not this proves successful, the wound should be packed with a one to-one mixture of sulphanilamide and sulphathiazole (Mackie *et al* 1945)

The prevention of the various skin lesions directly or indirectly caused by the diptera is mainly centred on the destruction of the larval and adult stages of the flies, and the protection of the human population by the use of mosquito nets, or screens of various types, and by the application of repellents The use of mosquito nets and screening is almost universal in the tropics, but is seldom employed in

this country where recourse is usually had to the use of repellents. The two outstanding repellents at present in use are oil of citronella and dimethyl phthalate both are effective against the common biting flies and each has its own advantages and disadvantages, but dimethyl phthalate, when properly used, has a more lasting effect than oil of citronella (Christophers, 1945)

ORDER ANOPLURA OR LICE

The lice which feed on man are permanent obligatory parasites, which rapidly perish when separated from their human host, and which cannot maintain themselves upon other animals. These facts explain their important role in epidemic disease transmission and the absence of reservoirs, other than the human, for the diseases they carry

The order includes only two species which are parasitic on man, the first of these, *Phthirus pubis*, the crab louse, is not known to transmit any specific infection to man, but the other species, *Pediculus humanus*, ranks next to the mosquito as a conveyer of epidemic diseases. Two varieties of the latter species are recognized and are named respectively *P humanus* var *capitis* and *P humanus* var *corporis*, but it is now generally considered that the morphological differences between them disappear on cross-breeding, and that each can adapt itself to the other's habitats and modes of life. Although these varieties thus closely resemble each other and have a world-wide distribution, nevertheless, the preponderance of one or other varies greatly under different climatic, racial and social circumstances. The head louse is abundant amongst persons in all countries, where the hair of the head is not cut short and where regular combing and cleanliness is neglected since this distribution is independent of clothing, the head louse may be as abundant amongst naked savages as amongst clothed Europeans. The body louse, on the other hand, can only survive if its human host wears some clothing (even beads will support a small colony), and it never produces a dense infestation unless the body is fully clothed and the washing facilities are limited. In civilized countries under normal conditions the body-louse problem, unlike the head-louse problem, is mainly confined to a definite class of impecunious feeble-minded or neglected persons. If, however national disasters, such as war or famine, occur the social conditions alter and the body louse thrives and spreads to hosts of a social status not previously affected, an increase which is often followed by outbreaks of epidemic louse-borne diseases, such as typhus and relapsing fever

The life-cycle of the body louse (*P humanus* var *corporis*) may be briefly summarized as follows. The adult female lays her eggs with great regularity at the rate of some 7-8 per day about 80 per cent of the eggs being attached to the clothing the remainder to hairs growing on the body The louse glues each egg, as it is laid, to a hair by a cement which dries rapidly is very strong, and resists solution by substances other than those which have a deleterious effect upon the skin. The egg shell also possesses great powers of resistance and is impenetrable to most, although not all, insecticides, except those likely to prove harmful to the host. In these circumstances the embryo louse, while in the egg, is to all intents and purposes immune from attack, so that recourse must be had to destruction of the active stages. These remarks, of course, only apply to eggs laid upon

the host, the destruction of eggs on clothing, separated from the host, being a relatively simple matter

The young louse emerges from the egg about the eighth day and takes about another eight days to reach maturity during which period it differs but little from its parents in form and habits. The mature louse lives for about a month and, in the case of the female lays some 150–200 eggs during its lifetime. Throughout the whole of its active life that is to say some five weeks, the louse feeds by piercing the skin of its host and probably partakes of its blood meal two or three times a day The fecundity of the louse, its close apposition to the skin, and its frequent intermittent feeding explain how it has acquired the unenviable reputation of being man's most troublesome ecto-parasite.

The life-cycle of the head louse (*P humanus* var *capitis*) differs but little from that of the body louse and, although the majority of the eggs are laid upon the growing hair of the scalp they may be, and often are, laid upon any head covering.

The signs and symptoms produced by the presence of lice on the human body vary very considerably but in the average individual the site of the bite, if examined immediately after the louse has fed is marked by a minute, flattened, red spot, whilst the swelling and irritation do not usually commence until a few hours later the latter sometimes persisting for several days The cause of the reaction is usually ascribed to the secretions of the salivary glands, but certain authorities (Peck *et al* 1943) believe that the faeces of the louse play an important role.

There is unquestionably a personal factor in the reaction of the individual to the presence of lice at one extreme are the hypersensitive individuals, at the other certain persons so tolerant that they may be unaware of their infestation. It is thought that the intensity of the reaction may alter in the individual in either direction, but although a few sensitive people may become more tolerant, the vast majority become increasingly sensitive.

The irritation caused by the presence of lice leads to scratching, which may be continued during sleep and may result in varying forms of secondary infection These secondary infections are generally presumed to be derived from organisms previously present in or upon the skin of the host, but there is some evidence that they may be transmitted directly by the feeding louse (Buxton 1939) The type and degree of these secondary infections varies with the density of the louse population the sensitivity of the individual his habits as regards cleanliness, etc., the duration of the infestation and its site. Thus eczematous infections of the scalp associated with cervical adenitis are not uncommon in head-lice infections, whilst long-continued heavy infestations with body lice may lead to the pigmented thickened skin associated with vagabond's disease

Diagnosis must rest upon the finding of the active forms, or the eggs of the louse on the clothing or on the person It is necessary to examine both clothing and persons, and advisable to remember that the eggs persist longer and are often more easily detected than are the active forms

The treatment of the lesions following lice infestations is, in our present state of knowledge, empirical and palliative and we need only concern ourselves with considering how to get rid of the infestation The literature on the subject is extensive, but the introduction of D D T has simplified matters and, although the

problems presented by the protection and disinfestation of large numbers of persons are still difficult and complex, it is generally agreed that for the treatment of the individual harbouring body lice the following will suffice. All clothing directly in contact with the skin should be freely dusted with a powder containing 10 per cent D.D.T. The treated clothing should then be worn for 10 days before sending it to be washed and laundered. If for any reason it is necessary to change the treated clothing before the expiration of 10 days the fresh garments should be similarly treated, and the discarded garments laundered and dusted with D.D.T. when returned. In the case of head-lice infestation a single treatment with 2 per cent D.D.T. in an aqueous emulsion is stated to secure a cure in every case where it is properly applied, and to provide protection against re-infestation for at least a fortnight. On the other hand, D.D.T. is not ovicidal, whereas the thiocyanates possess this property. It is possible, therefore, that the most rapid and certain method now in use is the application of Lethane 384 Special, diluted with an equal quantity of white oil.

The crab louse (*Phthirus pubis*) usually occurs on the hairs in the genital and peri-anal regions, but it may occur anywhere on the body including the eye-lashes, moustache and, although rarely, the scalp. The sluggishly moving adults and larvae, together with the eggs, are found attached to hairs in these regions: the eggs, unlike those of *Pediculus*, are never laid upon the clothing. This tendency of the crab lice to remain attached to the hair of the host generally results in the spread of infection by coitus, but if for any reason, such as scratching, the hairs which they are grasping become detached from the body, the lice are transported with them, and will subsequently leave them to seek a new host. This method of spread is unquestionably quite common and accounts for a considerable proportion of the infestations with crab lice.

The presence of crab lice is associated with similar lesions to those accompanying *Pediculus* infestations, although the irritation produced by the former is generally greater and in consequence the excoriations due to scratching are more severe. In addition to the lesions common to both *Pediculus* and *Phthirus* a certain proportion of persons infected with the latter exhibit peculiar blue spots 0·2–0·3 centimetre in diameter, which have been proved to be due to secretions from the salivary glands of the louse.

Formerly the treatment of crab lice involved shaving the infected region and the subsequent use of a mercury ointment. With the modern drugs now available it would seem that shaving is unnecessary and ointments, so far as mercury is concerned, are useless. D.D.T. and Gammexane are both effective against crab lice, whilst Mellanby (1944) reports complete cure following a single treatment with an emulsion of lauryl thiocyanate. There is always some risk of dermatitis when treating pediculosis of the ano-genital region, and it is well to remember that this may be caused by the vehicle as well as by the drug.

The great importance of lice in war-time has led to the publication of an extensive literature during the past six years. It is not possible to refer here to even the more important papers, but an admirable outline of the situation up to the outbreak of war is given by Buxton (1939), while subsequent developments up to the year 1945 are reviewed by Busvine (1945).

ORDER HEMIPTERA

The vast majority of the *Hemiptera* or bugs, are feeders on plant juices, but some of them, particularly those species occurring in the families *Cimicidae* and *Reduviidae* bite man and are of considerable medical importance. The members of the family *Cimicidae* which includes the common bed-bug (*Cimex* sp.), are not known to transmit disease in nature, but the family *Reduviidae* (cone-nosed or rapacious bugs) includes several species which, in addition to inflicting painful wounds in the skin are capable of transmitting South American trypanosomiasis, Chagas disease, to man the inoculated trypanosomes often causing a local reaction before the commencement of fever The life-cycles, habits, and control of the bed-bugs and of the rapacious bugs are somewhat similar and it is proposed only to consider the former genus which includes two common and almost identical species—*C lectularius* the common bed bug and *Cimex hemipterus* the tropical bed bug

Cimex lectularius has an almost world wide distribution although it is out numbered in the tropics by *C hemipterus* The adults and larvae are seldom seen in well lighted rooms, remaining concealed in cracks and crevices, from which they normally only emerge to feed under cover of darkness. The eggs are laid in the hiding places of the adults and are firmly attached to their sites by a cement produced by the female The eggs are easily visible to the naked eye and can at once be recognized since they have the shape of a flask, provided with a lid at the narrow end This characteristic form is of some importance, since the presence of the eggs provides valuable, often the only evidence of past or present infestation.

When investigating cases of dermatitis attributed to bed bugs, it is advisable to remember their powers of concealment and to realize that they will travel long distances, even crossing open spaces between houses, during their nocturnal search for food thus they may live in a neglected unoccupied room but dine in a well-kept and inhabited one. Under these circumstances it is wise not to dismiss too lightly a patient s complaint of being bitten by something at night even if careful search does not at first reveal the presence of bugs.

C lectularius, if deprived of its human host, will leave vacated rooms and establish itself temporarily in chicken runs, pigeon cotes, or animal houses, and these sources may in their turn lead to infestation of human habitations. Finally certain bugs which normally only bite birds (like *C columbarius* the pigeon bug, and the genus *Oeciacis* parasitic on swallows) may when the nests are deserted, invade houses and bite man (Chandler 1944) Bed-bugs can resist starvation for prolonged periods and there are many records of persons having been attacked after entering premises which had been left deserted for many months.

Bed bugs may of course, feed anywhere on the body but they tend mainly to attack the uncovered surfaces, so that the characteristic site of their bites are on the face and neck or uncovered portion of the hands and wrists of persons bitten when in bed Both sexes suck blood, a process which occupies some 3–8 minutes and which is usually painless and accompanied by no immediate reaction so that if as usually happens, it is inflicted at night, the actual bite may fail to wake the sleeper During the process of feeding the bug injects the contents of the salivary

glands the reaction to this fluid, which is usually delayed, varies with the susceptibility of the individual, but it generally results in a small hard swelling, at first whitish in colour later becoming inflamed and oedematous. The restlessness and loss of sleep due to the nightly attacks of bed-bugs, on persons sensitized to their saliva, may have a deleterious effect on the general health, particularly marked amongst children, as is evidenced by the improvement in their condition which often follows the successful extermination of the pest.

There is no specific treatment for the bites and there appear to be no records of successful desensitization indeed modern methods for ridding rooms of the bed-bug are so successful and relatively simple that such treatment of the individual appears superfluous.

Fumigation with hydrocyanic acid gas is highly effective and results in almost immediate destruction of all stages, including the eggs. Its use, however necessitates the employment of highly skilled, and therefore expensive, labour and is not devoid of risk. The simplest and, under certain conditions, the most effective method is to spray walls, furniture, beds, and mattresses with a 5 per cent solution of D D T in kerosene in such amount, that at least 100 milligrams of D.D T per square foot is deposited. Articles thus treated will remain free of bugs for sixty days or more. Similar or even better results have followed the use of Gammexane (Barnes, 1945 Burn, 1946), although it appears unlikely that its lasting powers will prove quite as great as those of D D T

ORDER SIPHONAPTERA

The order *Siphonaptera* (fleas) contains two families, the *Pulicidae* and the *Sarcopsyllidae* certain members of which are of particular interest to the dermatologist. The first-named family has a world-wide distribution, whereas those species of *Sarcopsyllidae* which parasitize man are confined to the tropics. Both families contain species which feed on man, but whereas the females of the *Pulicidae* usually leave their host to lay their eggs, the females of the burrowing fleas having fed, add injury to insult by penetrating the skin, and from this position pass their eggs to the exterior

The family *Pulicidae* contains a number of species which are responsible for the transmission of bubonic plague murine typhus, and, although rarely certain helminth infections to man. These diseases are confined for the most part to the tropics and subtropics, and in Great Britain the medical importance of fleas is confined to the irritation caused by their bites.

More than 1 000 species of fleas, some 50 of which occur in Great Britain, have been described from various mammalian and avian hosts. It is probable that most of these species will feed upon man, if forced to do so by being deprived of their normal and more congenial hosts the majority however only do so with reluctance and in practice the only fleas commonly attacking man are *Pulex irritans* and a limited number of species occurring on domestic stock and on domestic rodents. Thus, in Great Britain, complaints of flea nuisance are almost always traced to the human flea or else to the dog and cat fleas, *Ctenocephalides canis* and *C felis* These species have more or less similar life-cycles and habits,

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to flea-bites has been suggested, thus, Shannon (1943) has reported that thiamine chloride (vitamin B_1 hydrochloride), if given in a dose of 80–100 milligrams on the first day and about 10 milligrams per day afterwards, relieves the irritation of mosquito bites and prevents further biting. A year later Wilson *et al.* (1944) undertook a series of experiments, the results of which failed to substantiate Shannon's claim, in so far as the mosquito *Aëdes aegypti* was concerned. Later, however, Eder (1945), on the assumption that fleas attack certain persons and not others, concluded that thiamine deficiency might explain the difference, and therefore administered this drug to a series of persons of all ages, who had proved sensitive to flea-bites. According to Eder this treatment proved efficient not only in relieving the irritation, but also in reducing the number of bites received.

The possibility of desensitizing susceptible persons and subsequently immunizing them has been investigated by Cherney *et al.* (1939), McIvor and Cherney (1941 and 1943), and Hatoff (1946). As a result of their experiments these writers consider that the administration of flea antigen to susceptible persons is beneficial, the weals produced by subsequent flea-bites being smaller in size and persisting for a shorter period, during which there is a decrease of irritation and pruritus. It is interesting to note that in spite of this partial success, the authors failed to demonstrate complement fixing antibodies or precipitins in the blood of persons desensitized by the administration of flea antigen. This failure to demonstrate antibodies may have been due to the injection of insufficient antigen, for the total amount of salivary secretion injected by an insect during a series of bites is probably much in excess of what can be obtained from the glands after death.

When dealing with the flea as a vector of plague or murine typhus, special measures, chiefly directed against the rodent host, have to be studied. The following simple procedure will, however, usually suffice to deal with flea nuisance under normal conditions. The possible breeding places of the fleas, which have already been described, should be dusted with 5–10 per cent D.D.T. or Gammexane in an inert powder. If, as often happens, the source of infection comes from domestic pets, the powder should be well rubbed into their coats, whilst their living quarters should be thoroughly cleaned and freely dusted with the powder.

Family Sarcopsyllidae

The so-called jigger flea (*Tunga penetrans*) has a wide distribution in the tropics and subtropics, but has so far not invaded Europe. The life-cycle of the male is similar to that of a member of the *Pulicidae*, but the adult female, having fed on her host, burrows into the skin, usually somewhere on the undersurface of the foot, until the last abdominal segments are flush with the skin surface. The ova within her body now develop with great rapidity, so that within a week of penetrating the skin the tiny flea has become a circular object, often 6 millimetres in diameter. From now on the eggs are discharged from the flea's vaginal orifice and after falling to the ground, develop in a similar manner to those of the *Pulicidae*. The very serious dermal lesions which not uncommonly occur as sequelae to jigger infestations have been summarized by Gordon (1941), while Mackie *et al.* (1945) state that in Central America similar lesions may result in gas gangrene and tetanus.

but it is well to remember that they are not always confined to the same host, and that *P irritans* may be plentiful on the dog (MacArthur 1946) or on the pig (Freeman 1946)

The adult female commonly lays her eggs in such situations as the dust and dirt along walls, or in crevices between floor boards but, sometimes, they are laid on the fur or clothing of the host, from which since they are unattached, they fall to the ground From the eggs minute caterpillar-like larvae emerge, feed on organic matter in the surrounding dust and finally when full grown, spin cocoons within which they pupate. Normally the adults emerge from the cocoons after a few weeks but if left undisturbed the fleas may remain quiescent within them for as long as a year This habit explains why persons entering long-deserted houses are sometimes attacked by hordes of fleas

During the act of biting the flea injects the contents of the salivary glands, which usually gives rise to a haemorrhagic point surrounded by an erythematous and urticarial patch Since the flea is an easily disturbed intermittent feeder these reactions are often grouped in patches and may be arranged in lines. The irritation caused leads to scratching which may be followed by secondary infections.

It is persistently stated that certain individuals are not bitten by fleas and that if fleas alight on such persons, they tend to leave them while the only annoyance experienced is that caused by their movements on the skin— *Quant à moi ce n est pas la morsure c est la promenade* (Russell, 1913) Of others it is stated that they are constantly picking up fleas and that these insects bite them repeatedly and remain on their person until sought and destroyed. It is quite possible that this widespread belief that certain individuals are not bitten by fleas, is true, but there appears to be very little scientific evidence for its support. There is however much evidence that certain persons become sensitized to the salivary secretion of fleas and in consequence, react so violently to the bite that they cannot rest until the cause of the trouble has been removed.

As can well be imagined, persons who are sensitized to flea bites suffer such real discomfort that travelling, staying in hotels, visits to the theatre, etc., become viewed with justifiable apprehension This unhappy condition has led to considerable discussion not only of the nature of the condition, but of how best to avoid it by the use of repellents, etc. and of the most effective means of treating it, especially as regards the desensitization of susceptible persons This latter subject is of considerable general interest, since any such form of therapy which proves successful might be adapted to minimize the reaction following the bites of other species of blood-sucking insects

Repellents, such as dimethyl phthalate or oil of citronella, are probably of some value and should be applied to the socks or stockings and to the hems of trousers or skirts Powders containing D D T or Gammexane if sprinkled in the bed and underclothing, will certainly cause the death of fleas coming in contact with the drugs they have no repellent action, however and their lethal effect is not sufficiently rapid to prevent biting. As regards local therapy nothing specific appears to have been suggested and treatment consists in cleansing and disinfecting the site of the bite and applying some liquid or ointment that will relieve irritation and minimize resultant scratching. Oral treatment for those susceptible

deeper into the wound, and discharging more venom. It is for this reason that the popular belief that the sting should be immediately extracted is sound, although the methods recommended for its extraction are often unsatisfactory. Thus, grasping the protruding poison apparatus with forceps defeats its object by squeezing more venom into the wound, and in order to avoid this complication the sting should be scraped off the skin with a knife blade or needle.

The total number of bee stings necessary to produce death in a normal healthy adult has been estimated at some 500, if all the stings are administered at about the same time, but deaths from far fewer numbers have been recorded, not only amongst children, but also in a proportion of apparently healthy adults. On the whole, however, severe reactions following a limited number of stings only occur in sensitized persons. In such sensitized persons it is well known that the result of even a single sting, particularly if rapidly absorbed, may be followed by very serious and even fatal consequences. Such persons are in an unfortunate position, since, even if they can avoid a particular species of insect, like the bee, the poison injected by different members of the *Hymenoptera* is sufficiently similar to render the person allergic to many other species of stinging insects.

The treatment of bee stings in normal individuals consists in removing the stings and applying the customary local treatment, although the application of wet clay as advocated by some authors, can scarcely be recommended. In sensitized persons the sting should be extracted and the usual treatment for allergic reactions, including the giving of adrenaline, should be administered. Although the immediate condition may be thus alleviated, the only satisfactory prophylactic method of treating such persons appears to be the giving of a desensitizing course of bee venom, usually consisting of some 12–14 intradermal injections, commencing with $\frac{1}{1000}$ of a sting, and ending with a dose representing the total venom from a whole sting.

ORDER LEPIDOPTERA

The caterpillars of many species of butterflies and moths cause dermatitis of varying degrees of severity. The urticaria which follows direct or indirect contact with the larvae of such species as *Megalopyge opercularis* ("puss caterpillar") and *Euproctis phaeorrhoea* ("browntail moth"), is due to penetration of the human skin by hairs charged with poison from the subcuticular glands in the larvae. The lesions produced by these and other species of larvae are sometimes extensive, and when the insects occur in large numbers may cause local epidemics of some importance. Mackie *et al.* (1945) writing of the puss caterpillar state: "In certain parts of Texas thousands of cases of dermatitis have been known to occur in a single season, and public schools have been closed because of its abundance on playgrounds." There does not appear to be a specific method of treatment or of prophylaxis.

ORDER COLEOPTERA

Many beetles, particularly those occurring in the families *Meloidae* and *Staphylinidae* secrete a fluid which causes a blister on contact with the skin. This reaction is usually somewhat delayed, so that the patient is generally unable to associate the lesions with its cause.

Treatment in the early stages consists in aseptically removing the flea with its sac of eggs intact. Treatment in the later stages will of course, be dependent upon the nature and extent of the secondary infection

In order to avoid infection new comers to the tropics should be warned of the dangers of walking about in bare feet, and told of the importance of detecting and dealing with the jigger at as early a stage as possible. For destroying its free adult and larval forms the methods already recommended for the *Pulicidae* will suffice.

ORDER HYMENOPTERA

The order *Hymenoptera* includes all the four winged stinging flies, such as bees, wasps, hornets, and ants. Each of these groups comprises a large number of species, (thus more than 4 000 species of stinging bees are described) which differ somewhat as regards the severity of the reaction which follows the injection of their venom On the whole however the poisons secreted by different species of bees, wasps, and hornets are sufficiently similar to ensure that immunity to the poison of a species in one group will guarantee at least a partial immunity to the poison of a species in the same or another group whether a similar immunity is conferred against ant stings appears doubtful Much research, chiefly in connexion with bee venom has been carried out on the nature of the poison injected by the *Hymenoptera* nevertheless, its exact constitution is still unknown. It is frequently stated in text books, such as Craig and Faust s (1940) and Strong s (1945) that bee poison is related to rattlesnake and viper venom Feldberg and Kellaway (1937) have shown that cobra venom bee venom, and histamine all produce similar pathological lesions when injected intravenously and suggest that the two first named substances produce their effects by the liberation of histamine. That bee and viper venom although causing similar lesions, are not similar substances, is suggested by the work of Essex (1932) who proved that immunity to snake venom confers no immunity to bee-stings. It is clear from the publications of Phisalix (1922) that two distinct types of glands are concerned in secreting the poison the first contains a proportion of formic acid and the second, an alkaline substance sometimes described as a neuro-toxin furthermore, Phisalix and later writers have shown that whereas these two secretions are highly toxic when combined, they are only feebly so when injected separately It is possible that partial knowledge concerning this difference in the reaction of the two glands may be responsible for the many contradictory statements regarding the advisability of applying acids or alkalis to the site of the sting, some authorities going so far as to recommend an alkaline solution for bee stings, and an acid solution for wasp stings (Sibley 1933) Since the contents of the two glands are mixed at the time of injection, it is doubtful if the dermatologist can confidently recommend either form of treatment.

In normal individuals the severity of the reaction following the sting depends upon the amount of poison injected, which in its turn varies with the number of stings, and with the length of time that they are allowed to remain in the skin The sting of the bee, once inserted is anchored in the flesh, and this results in the whole tip of the abdomen which contains the poison apparatus, being torn away whilst the muscles attached to the apparatus continue to contract, forcing the dart

deeper into the wound, and discharging more venom. It is for this reason that the popular belief that the sting should be immediately extracted is sound, although the methods recommended for its extraction are often unsatisfactory. Thus, grasping the protruding poison apparatus with forceps defeats its object by squeezing more venom into the wound, and in order to avoid this complication the sting should be scraped off the skin with a knife blade or needle.

The total number of bee stings necessary to produce death in a normal healthy adult has been estimated at some 500, if all the stings are administered at about the same time, but deaths from far fewer numbers have been recorded, not only amongst children, but also in a proportion of apparently healthy adults. On the whole, however, severe reactions following a limited number of stings only occur in sensitized persons. In such sensitized persons it is well known that the result of even a single sting, particularly if rapidly absorbed, may be followed by very serious and even fatal consequences. Such persons are in an unfortunate position, since, even if they can avoid a particular species of insect, like the bee, the poison injected by different members of the *Hymenoptera* is sufficiently similar to render the person allergic to many other species of stinging insects.

The treatment of bee stings in normal individuals consists in removing the stings and applying the customary local treatment, although the application of wet clay as advocated by some authors, can scarcely be recommended. In sensitized persons the sting should be extracted and the usual treatment for allergic reactions, including the giving of adrenaline, should be administered. Although the immediate condition may be thus alleviated, the only satisfactory prophylactic method of treating such persons appears to be the giving of a desensitizing course of bee venom, usually consisting of some 12–14 intradermal injections, commencing with [illegible] of a sting, and ending with a dose representing the total venom from a whole sting.

ORDER LEPIDOPTERA

The caterpillars of many species of butterflies and moths cause dermatitis of varying degrees of severity. The urticaria which follows direct or indirect contact with the larvae of such species as *Megalopyge opercularis* (' puss caterpillar ') and *Euproctis phaeorrhoea* (' browntail moth '), is due to penetration of the human skin by hairs charged with poison from the subcuticular glands in the larvae. The lesions produced by these and other species of larvae are sometimes extensive, and when the insects occur in large numbers may cause local epidemics of some importance. Mackie *et al.* (1945), writing of the puss caterpillar state: "In certain parts of Texas thousands of cases of dermatitis have been known to occur in a single season, and public schools have been closed because of its abundance on playgrounds." There does not appear to be a specific method of treatment or of prophylaxis.

ORDER COLEOPTERA

Many beetles, particularly those occurring in the families *Meloidae* and *Staphylinidae* secrete a fluid which causes a blister on contact with the skin. This reaction is usually somewhat delayed, so that the patient is generally unable to associate the lesions with its cause.

OTHER VESICANT BITING OR STINGING CREATURES

The boundaries of parasitology are but ill defined and apart from those few common arthropods, worms and protozoa whose evil affects have already been described there is a host of other creatures of such varied forms as jelly-fishes, spiders scorpions molluscs, not to mention poisonous fishes, reptiles, and even mammals which damage the skin of man by means of stings, vesicant fluids, or poisonous bites To consider even a proportion of these would be a considerable task, and the reader must be referred to standard text books on the subject amongst which Phisalix (1922) still holds a well-earned position.

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THE DERMATOPHYTES

In Great Britain and the United States, the methods of treatment and control in pre-war decades had reduced the incidence of childhood ringworm infections to almost negligible proportions, but during the war years, probably because of the enforced relaxation of these controls, a striking increase of the infections, sometimes to the point of epidemics, occurred in both countries, and although the predominating species involved was *Microsporum audouini* a notably large proportion of the infections was caused by dermatophytes which are common parasites of the lower animals. Tinea pedis has also attracted increasing attention in recent years, especially in the armed Forces, the universities and other educa-



Fig. 19 — Chlamydospores in culture of *M. audouini*.

tional establishments and certain trades or industries, notably coal-mining. For the investigation and control of these infections a knowledge of the causative fungi is necessary but in studying the dermatophytes some difficulty may arise from the rather confused state of the taxonomy and nomenclature caused by the use of several different systems of classification and a multiplicity of synonyms. There is pressing need of simplification and standardization of the nomenclature of these fungi.

The first important classification of the ringworm fungi was presented by Sabouraud in his classical work *Les teignes* (1910). In this system generic

CHAPTER 10

MYCOLOGY IN RELATION TO DERMATOLOGY

J T DUNCAN

INTRODUCTION

THE study of medical mycology may be said to have originated during the period 1837–1845 in the work of Schönlein Remak Fuchs, and Langenberg in Germany and Gruby independently in France on the fungal nature of favus. Although priority of discovery may be accorded to the German group, Gruby s work, which embraced the other tineas and thrush was the more exact, complete, and far reaching In fact, Sabouraud in *Les teignes* (1910) states that *Gruby est l homme qui decouvrit l'origine mycosique de toutes les teignes humaines* Gruby created the genus *Microsporum* in 1843 and named the type species *Microsporum audouini* which was the first ringworm fungus to be named (*M audouini* was named after Jean Victor Audouin (1797–1841) a distinguished entomologist and an académicien in honour of his work on the muscardine disease of silk worms.) This very fruitful period in the history of medical mycology was followed by fifty years of steady progress in the understanding of ringworm disease and its causative fungi including the recognition of the disease in the lower animals its transmissibility to man, and the plurality of species of *Microsporum* and *Trichophyton*. With this pioneer work are associated the names of many eminent dermatologists who prepared the ground for Sabouraud s systematic study of the dermatophytes and ringworm which commenced in 1892 and culminated in the publication of his classic work *Les teignes* in 1910 Medical mycology had thus become an important department of dermatology but the discoveries of grave mycotic diseases affecting the deeper organs tended to broaden the field of interest in this branch of parasitology with a consequent orientation of the centre of interest a little out of the focus of the dermatologist. However if he could no longer claim medical mycology as simply a department of dermatology he did not relax his interest in the subject, for lesions of the skin may occur in any of the systemic mycoses in some they are relatively uncommon but in others they are so frequent as to be a characteristic feature of the disease. The trend in recent years has been towards a deeper interest in fungous diseases of the skin and a wider use of mycological methods in the study of these diseases. This is not merely a reflection of the new and widespread interest recently manifested in medical mycology but it is evidence of a growing appreciation, by dermatologists, of the importance of basing the diagnosis of fungous diseases on the identification of the causative fungus, often a very necessary step in connexion with the treatment and control of the disease and the study of its epidemiology as well as a safeguard against diagnostic error

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FIG. 19.—Chlamydospores in culture of *M. audouini*.

tional establishments and certain trades or industries, notably coal-mining. For the investigation and control of these infections a knowledge of the causative fungi is necessary but in studying the dermatophytes some difficulty may arise from the rather confused state of the taxonomy and nomenclature caused by the use of several different systems of classification and a multiplicity of synonyms. There is pressing need of simplification and standardization of the nomenclature of these fungi.

The first important classification of the ringworm fungi was presented by Sabouraud in his classical work *Les teignes* (1910). In this system generic

distinctions were based upon the morphology and the distribution of the fungus in parasitic life in the infected hair while species determination rested mainly upon the macroscopic characters of colonies vegetating on special culture media. The genera of Sabouraud's classification were *Microsporum* Gruby 1843 *Trichophyton*, Malmsten 1845 and *Achorion* Remak 1845 to these may be added two genera of dermatophytes which do not attack the hair *Epidermophyton* Lang, 1879, and *Endodermophyton* Castellani 1909 The genus *Trichophyton* was divided into three groups, according to the distribution of the parasitic spores on the hair *Endothrix* entirely intrapilary are essentially parasites of man *Neo-endothrix*, almost entirely intrapilary and *Ectothrix* mainly extrapilary are both parasitic on

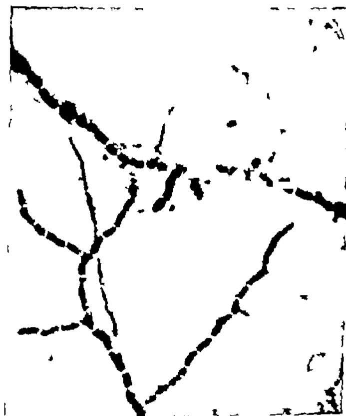


FIG. 20 —Arthrospores in culture of *T quinckeanum*.

the lower animals The *Ectothrix* group was further subdivided into a large-spore group called *Ectothrix-megaspores* and a small-spore group called *Ectothrix microides* and the divisions into species-groups and species were based upon culture characters.

Sabouraud s system has been adversely criticized by systematists on the ground that it is based partly upon clinical and partly upon botanical criteria. In fact, this criticism is a little unjust, for the genera are based not so much upon clinical reactions as upon the morphology of the parasitic form of the fungus—a necessary part of the general morphological study of a fungus which is essentially a parasite. A defect of Sabouraud s system is that it does not make use of the microscopic

morphology of the fungi in saprophytic life, although Sabouraud described this in connexion with many of the species. Another fault is that a species which may cause two different kinds of lesion falls into two different genera, e.g. *Trichophyton violaceum* and *Achorion violaceum*. However the principal defect of Sabouraud's system, and other systems, is that species-determination is based upon the macroscopic morphology of cultures, which is notoriously variable in the case of the dermatophytes. Emmons and Hollaender (1945), by irradiating the spores of a strain of typical *Trichophyton mentagrophytes* with sub-lethal doses of filtered ultra-violet rays, succeeded in obtaining 4 stable variants from the germination



FIG. 21.—Macroconidia (in thyrses) of *T. crateriforme*.

of the surviving spores. These variants, some of which were not unlike certain recognized species, showed no tendency towards reversion to the parent type during a period of 5 years observation in culture. It is not surprising that although Sabouraud in *Les teignes* listed only 45 species of dermatophytes, Gregory (1935), 25 years later was able to collect the names of 184 species from the accessible literature and there can be no doubt that the greater number of these specific names should be relegated to synonymy. Despite its defects, Sabouraud's system has proved of value in the past and none of the newer systems can wholly replace it in dermatological practice. The most useful outcome would be a combination

of the best feature of Sabouraud's system—the morphology of the fungi in parasitic life—with one of the simpler of the new botanical systems.

Before dealing with the botanical basis of classification of the dermatophytes it is necessary to consider however briefly those morphological characters of the fungi in culture to which taxonomic value has been accorded.

The chlamydospore

This resistant spore is formed by the migration of protoplasm and food material from neighbouring hyphal segments into a single segment which then becomes



FIG. 22.—Microconidia (in *grappe conidienne*) of *T mentagrophytes*

enlarged, thick walled, and differentiated from the parent hypha, to which, however it remains attached (Fig. 19) Chlamydospores may be terminal, in the continuity of the hypha, or sometimes lateral and they may be single or in short chains This kind of spore is common to all fungi and amongst the dermatophytes it is found chiefly in those species which form glabrous cultures or in strains which becoming pleomorphic, have lost the capacity to produce other spore forms.

The arthrospore

This kind of spore is formed in chains from the division of a fertile hypha, by transverse septa, into a number of short more or less cubical segments. These

segments become thick walled and may remain cubical or become ovoid or spherical, forming a chain of easily dissociated spores (Fig. 20). Arthrospores, in culture, are found chiefly but not only in species with glabrous colonies. In parasitic life this is the only kind of spore formed and it is common to all species of dermatophytes.

Conidia or aleuriospores

These are small spores arising from the sides and tips of hyphae or on short branches or pedicels. They are colourless, thin-walled and unicellular and they vary in shape from ovoid or spherical to pyriform or baton-shaped, and in size from to 4μ by 3 to 6μ. In some species, e.g. the endothrix trichophytons, they are spaced out along the sides of an undifferentiated parent hypha in the form acladium or thyrses (Fig. 21), but in other species, e.g. Sabouraud's gypseum group of ectothrix-microides trichophytons, they are borne abundantly on the short branches of bush-like sporophores, giving rise to clusters of spores—the *grappe conidienne* of Sabouraud (Fig. 22)—which, when very numerous, give the surface of the culture a characteristic powdery or chalky (gypseum) character

Macroconidia or pluriseptate spindles

These are large, elongated usually fusoid and multicellular spores, characteristic of the whole group of ringworm fungi, although in some species they are not

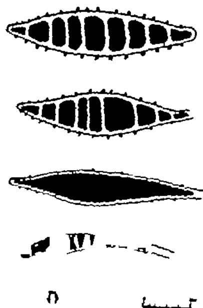


FIG. 23 Macroconidia of *Microsporum*.

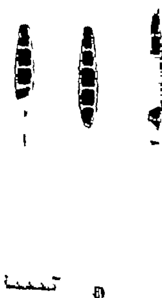


FIG. 24 Macroconidia of *Trichophyton*

common and in a few they are, as yet, unknown. Their shape and size are more or less characteristic in the three genera *Microsporum*, *Trichophyton*, and *Epidermophyton*. In *Microsporum* the spindle is large, thick-walled and symmetrically

fusiform tapering gracefully towards the ends, measuring 40–120μ in length by 7–30μ in greatest width and divided into separate segments by 6–15 transverse septa. The outer wall is usually decorated with tubercle-like prominences (Fig. 23) In *Trichophyton* the spindle may be more cylindrical or even distaff shaped It is thin walled and smooth and measures about 20–50μ in length by about 4–6μ in width with 2–6 transverse septa (Fig. 24). Its shape however tends to vary with different species-groups and in some species it may be relatively rare In *Epidermophyton* the characteristic spindle is pyriform to oval in shape, broadened and rounded at its distal pole, thick walled and smooth measuring about 40μ by 9μ Several may arise in a cluster from a

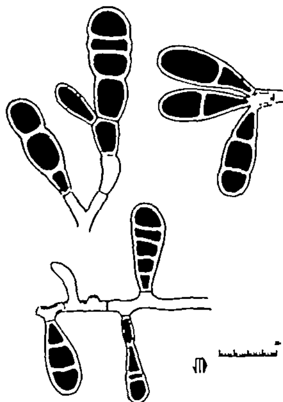


FIG. 25 — Macroconidia of *Epidermophyton*

common stalk and occasionally one may arise from a segment of another (Fig. 25). In the germination of a spindle each segment may behave as a separate cell. In addition to the spore forms there are certain mycelial structures, probably representing vestiges of the higher kind of reproductive apparatus of a hypothetical ascomycete ancestor of the dermatophytes, to which taxonomic importance has been accorded in some of the systems of classification These structures are (*a*) the nodular organ—a small knot of thickened, intertwining hyphal branches (Fig. 26) (*b*) the pectinate body—a short, thickened, curved hyphal branch, bearing from its convex side a number of abortive, irregular branches giving the whole structure an appearance suggesting a stag s antler (Fig. 27) and (*c*) the spiral hypha—a loosely or closely coiled hyphal branch resembling the tendril of a

climbing plant (Fig. 28). Davidson and Gregory (1937) have demonstrated an adhesive property of this structure and suggest that it may provide a means whereby a saprophytic growth of the fungus, say on stable refuse, might gain attachment to the hairs of an animal host. This suggestion opens up an interesting speculation on a possible natural saprophytic life of the ectothrix-microides group of trichophytons.

New or revised systems of classification many based upon the microscopic morphology of cultures, have been proposed by Ota and Langeron (1923),



Fig. 26.—Nodular organ in culture of T. mentagrophytes.

Grigoraki (1925 and 1929), Vuillemin (1925 and 1931), Nannizzi (1926), and Sabouraud (1929). Those founded upon Sabouraud's methods have perpetuated the faults of his original system and the purely botanical systems of classification, however interesting and ingenious, have usually been based upon inconstant and variable morphological characters which render them impracticable. An effect of so many new systems of classification has been to increase the confusion of the nomenclature by multiplying and duplicating generic names. Langeron and Milochevitch (1930), from a study of the higher morphological development attained by cultures of the dermatophytes on certain natural media such as barley

or wheat grains or on agar media with a polysaccharide base, proposed a new classification based upon the microscopic morphology developed by their methods of culture They place the dermatophytes in the Class of *Ascomycetes*, the Order of *Plectascales* and the Family of *Gymnoascaceae* with 4 genera

Ctenomyces Eidem 1880 emend Langeron and Milochevitch, 1930, embracing the ectothrix microides group of trichophytons, which stand apart from the other dermatophytes.

Sabouraudites Ota and Langeron 1923 emend Langeron and Milochevitch, 1930 which includes species of the old genus *Microsporum*, with such species as *Achorion quinckeanum* of the mouse and *Achorion gallinae* of fowls.

Epidermophyton Lang, 1879 which has only one known species, *Epidermophyton floccosum* (Harz, 1870) Lang, 1879 (*Synonyms E. cruris*, *E inguinale* etc)

Trichophyton Malmsten 1945 emend Langeron and Milochevitch, 1930, nec Ota and Langeron 1923 which embraces all the dermatophytes



Fig 27 —Pectinate body

not belonging to one of the other genera It includes the typical trichophytons of the large spore groups and certain species of poor morphology such as the former *Achorion schönleinii Microsporum ferrugineum*, and *Endodermophyton concentricum*

The system of Langeron and Milochevitch, which is used in many European countries has not received universal acceptance

Emmons (1943) has put forward a simplified and rational system of classification which is not incompatible with the original classification of Sabouraud. He proposes 3 genera based upon the characters of the Macroconidium (which are described on p 217) *Trichophyton Microsporum*, and *Epidermophyton*. In preserving the old familiar nomenclature he has re-defined the generic names, shifting the emphasis from the clinical characters of the infection to the cultural characters of the fungus The disappearance of the genus *Achorion* removes a source of confusion and the Endodermophytons have been restored to their proper place in *Trichophyton* Sabouraud (1929) condemns the practice of approaching the problem of classification either from the purely clinical or purely cultural standpoint, and he pleads for closer co-operation between the mycologist and the dermatologist Sabouraud s classification cannot be considered wholly obsolete while the diagnosis of tinea is made on the microscopic examination of infected hairs, and the time is opportune for the reconcilement of a modified Sabouraud system with the classification proposed by Emmons.

A good effect of the recent studies upon classification and nomenclature has been the weeding-out of many redundant specific names, so that the 184 specific names referred to by Gregory (1935) may well be represented by the 19 dermatophyte species accepted by Langeron (1945). However in relegating to synonymy so many specific names, care should be taken to preserve the identity of stable varieties, the recognition of which may be of great importance in epidemiology *Microsporum canis* is a frequent parasite on children and it has 3 well characterized varieties, one non pigmented and forming lanose colonies, another flat and secreting a rich orange pigment which diffuses into the culture medium, and the third



Fig. 29.—Spiral hyphae in culture of *T. mentagrophytes*.

developing an undiffused primrose yellow pigment. All 3 varieties occur separately in neighbouring areas in southern England.

As a test of specific relationship, hyphal fusion between the mycelia of two separate dermatophyte strains, vegetating together in hanging-drop microculture, has been advocated by Davidson, Dowding, and Buller (1932), and it may be urged that evidence of this kind be obtained before assuming that two differently named dermatophytes are in fact one species.

PARASITISM OF THE DERMATOPHYTES

The dermatophytes are amongst the more highly parasitic of the pathogenic fungi and they have developed a very marked degree of host specialism. Certain

species, e.g. *Microsporum audouini* are parasitic only on man and the infection is transmitted from child to child with no known period of saprophytic life intervening yet this fungus, which during centuries may have vegetated only as a parasite can with remarkable facility adapt itself to saprophytic life when placed upon a suitable medium It seems possible, however that some of the species which are parasitic on the lower animals, such as *Trichophyton mentagrophytes* on the horse, may have transient periods of saprophytic life upon such materials as stable refuse and from this environment they may return to parasitism on a new animal host Confirmation of this supposition might explain the higher morphological development in culture of some dermatophytes parasitic on the lower animals in comparison with those essentially parasitic on man

All ringworm fungi which infect the hairs of man except *Trichophyton schönleinii* the cause of favus, vegetate within the hair shaft, forming a zone of growth— Adamson s fringe —near its junction with the vital bulb From this zone of vegetation hyphae arise which may remain within the hair shaft or pass on to its exterior but in both cases, the hyphae immediately break up into chains of spores—intrapilary or extrapilary As the hair bulb is not invaded the growth of the hair continues and the spores of the parasite are carried to the surface from which they may be dispersed to new hosts. Situated within the hair shaft, near the fundus of the follicle, the vegetating zone of the fungus is inaccessible to fungicides applied at the skin surface, so the host affords the parasite protection and assists the propagation of its kind In the case of the strictly human parasites, *Microsporum audouini* and the endothrix trichophytons, a state of almost perfect host parasite equilibrium is established and the infection of the hair provokes no hostile response from the host in fact the parasitism persists until it is terminated spontaneously during adolescence, possibly in connexion with the functional maturation of the reproductive organs In the case of alien parasites, however such as *T mentagraphytes* a host parasite balance is not established and a simple or suppurative folliculitis, which may take the form of sycosis, kerion, or agminate folliculitis, leads to the shedding of the infected hair and natural cure. With *Microsporum canis* another alien parasite a state of host-parasite equilibrium may be established but it is frequently unstable, so that the application of a stimulating treatment to the scalp may provoke an inflammatory reaction and expulsion of the infected hair In some cases, however *M canis* may be, parasitically as efficient as *M audouini* and recourse must be had to epilation by x rays.

Clinically even in the absence of kerion *T mentagraphytes* infection can easily be distinguished from the *Microsporum* infections by the fluorescence test, but neither by clinical inspection nor by microscopy can some cases of tinea capitis caused by *M canis* be distinguished from that due to *M audouini* although associated skin lesions or a very marked epithelial reaction would suggest the animal *Microsporum* Only by isolation in culture can the identity of the parasite be determined Comparing these 3 species in scalp infections on the child *M audouini* the specific parasite, is transmitted from child to child and is the most infective and the least pathogenic of the three *T mentagraphytes* which is transmitted from the animal host or some associated source and shows little tendency to further transmission from child to child, is the most pathogenic *M canis*,

although an alien parasite, is transmissible from child to child but probably only for a limited number of transfers, so that occasional renewal of the infection from the animal reservoir appears to be necessary for the continued propagation of the disease on children—it is therefore less infective although usually more pathogenic than *M. audouini*. Selective infectivity of a high order would seem to be the characteristic of the specific parasite, while pathogenicity suggests the ill-adapted alien, or in other words, pathogenicity tends to diminish as selective infectivity increases. However in epidemics of ringworm caused by *M. audouini* moderately severe lesions may develop and sometimes an adult may be infected, but the greater virulence of the infection may be, in some measure relative to the lowered resistance of the potential hosts. The treatment of tinea capitis caused by *M. canis* may be said to be simplified in so far as a proportion of the cases will yield to locally applied medicaments, but the control of this alien infection is complicated by the existence of an animal reservoir host which may be difficult to detect.

TINEA PEDIS

The importance of tinea pedis in the armed Forces, in universities and other educational establishments which encourage athletic games, and in certain industries, notably coal-mining, cannot be gainsaid, and there is no doubt that war-time conditions, especially the mobilization and training of armies, are conducive to the dissemination of the infection and to the importation of new infections by the movements of troops. Yet it has been said that the problem of tinea pedis is exaggerated and, in support of this view it must be admitted that statements of the incidence of the disease in communities are frequently based upon very untrustworthy data.

There are 3 methods of diagnosing tinea pedis by clinical inspection, by microscopy and by isolation of the causative fungus in culture. The results of these 3 methods applied to the same group of patients may show marked disparity. Strickler and Friedman (1931), quoting Hulsey and Jordan (1925), state that although 67 per cent of a group of students had clinical tinea pedis, only 47 per cent were positive by microscopy and only 5 per cent by culture. Peck, Botvinick, and Schwartz (1944), were able to cultivate the fungus from only 19 per cent of 231 clinically positive cases, and Hopkins and his colleagues (1944) found that 30 per cent of lesions of the feet in military personnel were microscopically negative for tinea pedis and were caused by coccal infections, allergy chemical irritants, hyperidrosis, trauma, or hypostasis. Mycological examinations have shown that some severe lesions of the feet may not be mycotic and some clinically trivial lesions may be tinea pedis, not only infective but capable of flaring-up into a severe form under conditions of service in hot climates. Therefore, it cannot be urged too strongly that when collecting data for statistical analysis, the diagnosis of tinea pedis must be based upon a proper mycological examination, microscopical or cultural, or preferably both.

For mycological examination, material should be selected with care. After a preliminary cleansing of the part by swabbing with 70 per cent alcohol, a scraping should be taken from the active margin of a spreading lesion or a scaling area.

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culture are more alkali-tolerant than many of the common moulds. A 4 per cent maltose-agar medium of the Sabouraud type, in the form of plates, freshly set to a reaction of pH 10·5, is sown with the material under examination and incubated at 30° C. instead of 22° C. The combination of relatively high pH and temperature inhibits the growth of many common moulds, especially species of *Penicillium* and the growth of species of *Aspergillus* and *Mucor* which are relatively thermophylic, is retarded so that the young colonies of the dermatophyte can be detected and picked off for subculture before the plate is overgrown by the mould. Using carefully selected material for sowing, and the culture technique described, the results of diagnosis by culture should approximate closely to those by microscopy

Dermatophytes causing tinea pedis and epidermophytosis

The three important dermatophytes causing tinea pedis and epidermophytosis are, *Trichophyton interdigitale* (synonyms, *T. mentagrophytes*, *T. asteroides*, etc.), *Trichophyton rubrum* (synonyms, *T. purpureum*, *T. plurizoniforme* etc.) and *Epidermophyton floccosum* (synonyms, *E. cruris*, *E. inguinale* etc.). *T. interdigitale* may form white, cottonous, or chalky colonies, often brownish or reddish on the reverse surface. Microscopically it presents the morphology of the ectothrix microides group with short, branching sporophores bearing very numerous conidia, en grappe macroconidia may be few and rather stumpy the vegetative mycelium shows very thick and very slender hyphae, and spiral hyphae may be numerous. *T. rubrum* is a polymorphic species which may form flattened, red-dish-purple colonies covered with a light, white powder or down (*T. purpureum*) which, on microscopical examination is seen to consist of mycelium bearing enormous numbers of slender cylindrical macroconidia, often bearing terminal filaments. More frequently the colony may be white and cottonous with a deep crimson reverse surface (*T. rubrum*) the crimson pigment diffuses into the culture medium and the aerial mycelium may take on a rose-pink colour. Microscopically the mycelium is seen to bear slender or baton-shaped microconidia arranged in thyrses, but macroconidia are rare or absent. In a third form the colony may be white, cottonous and unpigmented and microscopically showing only a few very slender baton-shaped or almost bacilliform microconidia. In a fourth form the colony may be cottonous and presenting alternating, concentric rings of purple or red and pink or white (*T. plurizoniforme*). The microscopic morphology is similar to that of the *T. rubrum* type. *Epidermophyton floccosum* develops, in primary culture, a flat, buffy or yellowish colony powdery or downy on the surface, and, microscopically consisting of masses of the characteristic macroconidia, pear-shaped or oval, arising singly or in bunches from the hyphae in subcultures the colonies are cottonous and white or yellowish with a yellow reverse surface. The characteristic macroconidia are still present but fewer microconidia are never found.

C ro (1944) and Montgomery and Casper (1945) assert that the lesions on the foot caused by the three species of dermatophytes just described are so characteristic of the causative fungus that the species can often be identified by inspection of the lesion. Weidman and Glass (1946) have not been able to confirm this opinion nor the more widespread one, that infections by *T. rubrum* are especially difficult to cure.

If there is much thickened sodden skin between the toes, the scraping may be made near the margin of the area, where it adjoins the healthy skin, and in vesicular lesions the skin forming the dome of the vesicle should be snipped off For microscopical examination the material including nail clippings, should be teased out on a glass slide in a few drops of aqueous 5-20 per cent solution of potassium hydrate, covered with a coverslip and allowed to macerate, with or without the aid of gentle warming. In a suitable preparation the fungal mycelium should be seen as a network of highly refractile ramifying, septate hyphae breaking up in places into files of cubical spores against the flat background of macerated epithelial cells. An error in diagnosis by the inexperienced may arise, although rarely from the presence of the mycelium of some saprophytic fungus, but more frequently from artifacts resembling fungal elements, such as the mosaic fungus which Davidson and Gregory (1935) have shown to be formed of aggregations of fine crystals of cholesterol usually following the outlines of the epithelial cells, not caused by the action of the caustic potash solution Skin and other epithelial tissues, when macerated in strong alkaline solutions, may show particles of highly refractile lipoid material simulating yeasts or mycelium but the lipoid is soluble in alcohol and is not stained by aniline dyes For more permanent mounts, lacto-phenol may be used in place of the caustic potash solution but the definition of the fungus will be much less sharp Alternatively the specimen may be fixed and stained by Gram s method or by Sahli's borax blue.

In a broad sense it may be said that the disparity between the results of clinical and of carefully conducted microscopical examinations may be accepted as a measure of the clinical error

Cultivation of the fungus

Cultivation is necessary for the specific identification of the causative fungus, and it affords unequivocal diagnostic evidence. Isolation of the fungus in culture is often made difficult, however by the presence of contaminating bacteria and moulds and, after making allowance for cases in which as a result of fungicidal treatment, the fungus seen in the scales is no longer viable, the disparity between the microscopically and the culturally positive results must be attributed to faulty culture technique. In isolating the dermatophyte from contaminated skin scales, the preliminary swabbing with 70 per cent alcohol serves to destroy some of the bacteria but prolonged exposure to 70 per cent alcohol may kill the dermatophyte. Skin scales for culture should be finely teased out and the sowings spaced apart on the culture medium. If mould contamination is suspected it is advisable to use a plate medium instead of a slant. The acid reaction (about *p*H 5·0) of the common mycological culture media will inhibit the growth of many bacteria but it is usually necessary to employ an additional enriching factor and for this purpose sodium tellurite added in the proportion of 1 8 millilitres of a 2 per cent aqueous solution to 100 millilitres of the agar medium is especially useful. For tellurite resistant bacteria penicillin may be used for the preliminary treatment of the skin scales or as an addition to the solid agar medium By these means bacterial contaminants are usually overcome, but none of them will prevent the growth of contaminating moulds. For this purpose, Leise and James (1945) devised an alkaline medium based upon the observation that dermatophytes in

for footwear is engaging the attention of leather manufacturers in the United States of America

In the epidemiology of tinea pedis, circumstantial evidence points very strongly to the communal shower or bathing room as the source of infection, and it is generally accepted that infection takes place by picking up between the toes, and especially between the fourth and fifth toes, infective material deposited on the floor by another bather On the other hand, Peck, Botvinick, and Schwartz (1944) found that the incidence of clinical tinea pedis was no greater in a group of workers in factories in which the use of shower baths was compulsory than in another group of employees for whom bathing facilities were not provided. In the same investigation, an attempt was made, but without success, to cultivate ring worm fungi from swabbings of the shower room floors. Uncontrolled observations of this kind should not discount the danger of the shower room, but they may serve a useful purpose in directing attention to the many other means of transfer of infective material from the feet of the diseased to those of the healthy

MONILIASIS

The dermal, intertriginous, paronychial, and onychial lesions of moniliasis are so familiar that no clinical description is needed, but care should be taken to distinguish them from types of tinea and, to ensure this, a proper mycological examination, including both microscopy and culture, should be made such an examination would also serve to identify those rarer dermal mycoses such as geotrichosis and the dermal forms of torulosis and sporotrichosis which may not be clinically distinctive. The genus *Candida* (synonym, *Monilia*) is easily identified microscopically in preparations from the lesions, by its septate, branching mycelium about 2 3μ in diameter bearing clusters of budding yeasts, 3-5μ in diameter from the distal poles of the mycelial segments. The fungus is easily isolated in culture by sowing the morbid material on beer wort-agar or if there is much bacterial contamination, in Raulin s fluid, as a preliminary to plating out on beer wort-agar or glucose-agar and incubating the cultures at 37° C In culture, the genus is distinguished by a branching, septate mycelium bearing elongated or rounded budding cells in simple or composite verticils from the distal poles of the mycelial segments. The character of the erticil depends largely upon the species of *Candida* but it may be influenced by the composition of the culture medium. The best morphological development is found in cultures in the potato-extract med um of Langeron and Talice (193), or in the submerged part of the growth on glucose-agar or maltose-agar Ascospores are not formed in this genus and the examination to exclude these spores should be undertaken by a competent mycologist Langeron and Guerra (1938) recognize sixteen valid species of *Candida* but only two species, *Candida albicans* (Robin) Berkhout and *Candida tropicalis* (C tellan) Berkhout, are known to be of pathological importance. The identification of pecies is based partly upon morphological features, but chiefly upon tests of sugar fermentations similar to those used in bacteriology and the auxanographic method of Beijerinck, described by Lodder which is a test of the capacity of the fungus to utilize in egetation certain carbon and nitrogen containing compounds, as the only available sources of these necessary elements.

Double infections, such as infection of the nails by *T rubrum* and of the inter digital clefts by *E floccosum* are not rare.

Treatment

It cannot be said that the present treatment of tinea pedis is wholly satisfactory and despite an imposing array of medicaments, cure is sometimes difficult and is not always attained Roughly the rationale of treatment falls under three headings (*a*) mild forms of treatment directed primarily to the alleviation of symptoms and complications (*b*) the mechanical removal of the fungus with the infected tissue, and (*c*) the use of fungicidal preparations aiming at the cure of the disease by destruction of the fungus *in situ* In category (*b*) may be included Whitfield's ointment the ethyl chloride spray treatment advocated by Lewis and Morgenson (1944) a number of other vesicants and the surgical evulsion of infected nails. There is no doubt of the usefulness of Whitfield s ointment and the relief derived from a light frosting by ethyl chloride is very impressive, but relief of signs and symptoms does not necessarily imply cure, and the disease may relapse. In category (*c*) are included a number of efficient fungistatic and fungicidal substances, some of which have proved unsatisfactory because anti-fungal properties are frequently associated with irritant or sensitizing action Of the newer fungicides, the mercurials, especially the phenylmercuric compounds, and the salts of some of the long chain unsaturated fatty acids notably propionic and undecylenic acids have attracted much attention Keeney Ajello Broyles, and Lankford (1944), have demonstrated *in vitro* the fungistatic superiority over Whitfield s ointment, of ointments containing propionates and undecylenates, and it is claimed that these ointments may be used continuously over long periods in treatment, without danger of irritation or sensitization The propionate has an added advantage in being bacteriostatic against the skin cocci Notwithstanding the recent advances in the study of fungicides, this research should not be relaxed, but new groups should be explored and tests of their fungistatic and fungicidal powers made, *in vitro* preferably by a simple method such as that of Burlinghame and Reddish (1939) The research should not, however be confined to chemical fungicides, but the potentialities of natural antibiotics should also be examined such as the antibiotic substance active against *Trichophyton mentagrophytes* which Lewis, Hopper and Schultz (1946) demonstrated in cultures of a particular strain of *Bacillus subtilis* In judging the value of any therapeutic agent against tinea pedis, it should be remembered that the treatment must be adapted to the clinical condition obtaining, e g. the early uncomplicated, superficial infection of the skin which may yield quickly to any efficient fungicide the acute, inflammatory or complicated lesion on which any active fungicidal treatment is contra indicated until the danger of irritation and sensitization has been removed and finally the hyperkeratotic and more chronic cases with infection of the nail in which the physical obstacle to the penetration of the fungicide must be overcome.

In addition to the therapeutic application of fungicides, Peck Botvinick and Schwartz (1944) have shown that there is still a field for research in the preventive fungicidal treatment of the floors, and the provision of efficient prophylactic foot baths in communal bathing rooms The production of a fungus-resistant leather

fungus *Coccidioides immitis* in the desert soil is replenished and that the spores of the fungus, carried with the wind-borne dust during the dry season, are inhaled by man, causing primary pulmonary coccidioidomycosis. Infection may also take place, although rarely by inoculation through the skin. Only about one case out of several hundred, of the mild primary disease, develops to the grave coccidioidal granuloma stage. The causative fungus of sporotrichosis, *Sporotrichum schenckii*, has been found as a saprophyte upon various vegetable substrata such as sphagnum moss, berberis, and horse-tails and also in the nests of insects and the hides of rats and horses, both of which animals suffer from sporotrichosis. Infection may be derived from any of these sources and the mode of introduction is by thorn prick, through an open wound in the skin, by insect bite, or possibly from infection through a hair follicle. du Toit (1942), in a unique experience of 650 cases in a South African mine, found that the infection had always been contracted in the mine and a saprophytic growth of Sporotrichum on the mine timbers was suspected

Chromoblastomycosis, caused by *Phialophora verrucosa* P *pedrosoi* and P *compacta* is another disease which has aroused much interest recently chiefly in connexion with the elucidation of its mycology by Emmons and Carrion (1936) and Negroni (1936), and the discovery of the infection in new areas, including South Africa and Australia. Species of *Phialophora* have been found as saprophytes on forest timber and the mode of infection of the skin is by inoculation on trauma. The North and South American types of blastomycosis, caused respectively by *Blastomyces dermatitidis* and *Paracoccidioides brasiliensis*, are confined to those continental divisions, and *B. dermatitidis* is believed to vegetate upon timber Infection, in the North American type is, in the majority of cases, by inhalation of the saprophytic spores and in a smaller number of cases by inoculation through the skin, while the buccal mucosa is suspected as the portal of entry in the South American disease The causative fungus of torulosis, *Cryptococcus neoformans* has been found in milk products and other foodstuffs, and the path of infection may be through the mouth or through the skin, but, although evidence is lacking, a more important path may be through the lungs, from inhalation of the dried torula cells. The epidemiology of histoplasmosis, a disease of world-wide distribution is still unknown, and the causative fungus *Histoplasma capsulatum* has only been found in the naturally acquired disease in man and dogs, but there is no evidence that the dog is the reservoir of the human infection. Recent observations on the results of skin sensitivity tests with histoplasmin by Palmer (1945 1946) and by Christie and Peterson (1945 1946) suggest the possible existence of a mild, but as yet unrecognized, form of histoplasmosis. The epidemiology of the systemic mycoses offers a wide and largely unexplored field to the investigator

The skin lesions in systemic mycoses

In sporotrichosis, the subcutaneous gumma, involving the skin and projecting on the surface as a small, violaceous, elastic, or fluctuant tumour or after breaking down, a a thick-walled, indolent ulcer with granulating base discharging mucoid, yellow pus, and the frequently associated lymphangitis with its chain of secondary gummata in the course of the affected lymphatic vessel are well known, despite the rarity of the disease The disseminated form with multiple, small, subcutaneous

Serological methods are rarely used for the differentiation of species, but antigenic differences may be demonstrated by quantitative precipitin tests. The following sugars are fermented with gas formation by *Candida albicans* glucose, maltose, galactose, and laevulose, but not saccharose, mannitol or lactose. *Candida tropicalis* ferments those substances fermented by *C albicans*, and saccharose in addition In recording fermentations by these fungi only readings of gas formation and not changes in reaction are taken By the auxanographic method both species are shown to be capable of utilizing, as sources of carbon—dextrose, laevulose, mannose, galactose, maltose, and saccharose but not lactose, and as sources of nitrogen—asparagine, ammonium sulphate, urea and peptone but not potassium nitrate. The infection in dermal moniliasis may be derived from thrush lesions of the mouth or the genitalia, or from *C albicans* vegetating as a commensal in these situations or the intestine, and, in treating the disease, the probable source of the infection as well as any predisposing condition such as diabetes, should also receive attention. It is sometimes contended that although *C albicans* is a frequent inhabitant of the healthy mouth it is not found on healthy skin and this view receives some support from the work of Benham and Hopkins (1933), who failed to find the species amongst various yeast like fungi isolated from the skins of 100 healthy persons. For this reason the mere presence of *C albicans* on a skin lesion is frequently accepted as aetiologically significant, although the possibility of contamination of a non mycotic skin lesion by *Candida* vegetating in the mouth and the other situations mentioned cannot be denied.

The value of serological tests or dermal sensitivity tests with *Candida* antigens, in the diagnosis of moniliasis, is vitiated by the tendency for positive results to be given in the case of healthy persons harbouring the fungus in the alimentary canal or elsewhere

THE SYSTEMIC MYCOSES

In contrast to the dermatophytes which are highly parasitic epiphytes transmitted directly from host to host and exhibiting only a moderate degree of morphological modification in parasitic life, the fungi causing systemic mycoses are usually dimorphic they vegetate saprophytically in a more or less complex mycelial form on plants or on inanimate substrata, but for parasitic life in the deeper tissues of animals they are capable of morphological adaptation to a simple, frequently unicellular and yeast like form suitable for rapid reproduction and invasion. The recognition of two different forms of the fungus, in the lesion and in culture, is vitally important in diagnosis. The systemic mycoses are never or very rarely transmitted directly from host to host although such transmission is possible experimentally but infection is by the saprophytic form In some systemic mycoses, e.g. histoplasmosis, the source and the mode of infection are not known but the elucidation of the epidemiology of this group of diseases is making good progress In the case of coccidioidomycosis, the recent work of Dickson and Gifford Aronson Emmons, Smith and others has shown that the disease is highly infectious and common in its mild primary stage in endemic areas in the desert country of the South Western United States that certain desert rodents, notably kangaroo rats and pocket mice, harbour the infection and may constitute a necessary animal reservoir of the disease from which the saprophytic growth of the

fungus *Coccidioides immitis* in the desert soil is replenished and that the spores of the fungus, carried with the wind-borne dust during the dry season, are inhaled by man, causing primary pulmonary coccidioidomycosis. Infection may also take place, although rarely by inoculation through the skin. Only about one case out of several hundred, of the mild primary disease, develops to the grave coccidioidal granuloma stage. The causative fungus of sporotrichosis, *Sporotrichum schenckii*, has been found as a saprophyte upon various vegetable substrata such as sphagnum moss, berberis, and horse-tails and also in the nests of insects and the hides of rats and horses, both of which animals suffer from sporotrichosis. Infection may be derived from any of these sources and the mode of introduction is by thorn prick, through an open wound in the skin, by insect bite, or possibly from infection through a hair follicle. du Toit (1942) in a unique experience of 650 cases in a South African mine, found that the infection had always been contracted in the mine and a saprophytic growth of Sporotrichum on the mine timbers was suspected.

Chromoblastomycosis, caused by *Phialophora verrucosa* *P pedrosoi* and *P compacta* is another disease which has aroused much interest recently chiefly in connexion with the elucidation of its mycology by Emmons and Carrion (1936) and Negroni (1936) and the discovery of the infection in new areas, including South Africa and Australia. Species of *Phialophora* have been found as saprophytes on forest timber and the mode of infection of the skin is by inoculation on trauma. The North and South American types of blastomycosis, caused respectively by *Blastomyces dermatitidis* and *Paracoccidioides brasiliensis*, are confined to those continental divisions, and *B dermatitidis* is believed to vegetate upon timber Infection in the North American type, is, in the majority of cases, by inhalation of the saprophytic spores and in a smaller number of cases by inoculation through the skin, while the buccal mucosa is suspected as the portal of entry in the South American disease The causative fungus of torulosis, *Cryptococcus neoformans*, has been found in milk products and other foodstuffs, and the path of infection may be through the mouth or through the skin, but, although evidence is lacking, a more important path may be through the lungs, from inhalation of the dried torula cells. The epidemiology of histoplasmosis, a disease of world-wide distribution is still unknown, and the causative fungus *Histoplasma capsulatum* has only been found in the naturally acquired disease in man and dogs, but there is no evidence that the dog is the reservoir of the human infection. Recent observations on the results of skin sensitivity tests with histoplasmin by Palmer (1945 1946) and by Christie and Peterson (1945, 1946) suggest the possible existence of a mild, but as yet unrecognized, form of histoplasmosis. The epidemiology of the systemic mycoses offers a wide and largely unexplored field to the investigator

The skin lesions in systemic mycoses

In sporotrichosis, the subcutaneous gumma, involving the skin and projecting on the surface as a small, violaceous, elastic, or fluctuant tumour or after breaking down as a thick walled, indolent ulcer with granulating base discharging mucoid, yellow pus, and the frequently associated lymphangitis with its chain of secondary gummata in the course of the affected lymphatic vessel are well known, despite the rarity of the disease The disseminated form with multiple, small, subcutaneous

gummata which may or may not break down and the visceral form of the disease with involvement of the mucosae and the underlying cartilaginous and bony structures, the skeletal tissues, the testes and the lungs, as well as the very superficial lesions involving the skin only are less well known The superficial dermal lesions, often primary may take the form of flat warts of a violet tint, well defined but with rather irregular outline and scaly surface, occurring especially upon the face, or of a *superficial granulomatous plaque* or a scaly patch resembling ringworm. Some of these lesions are purely epidermal but others involve the corium. du Toit (1942), from his unique experience of the disease, suggests that the superficial character of the lesion is a measure of the resistance of the host to the infection the greater the natural resistance the more superficial will be the lesion and the greater the tendency to spontaneous cure The diagnosis of sporotrichosis of any type depends upon the isolation of *Sporotrichum schencki* in culture from the lesion, and this is easily achieved even when as is almost invariable in the human lesions, *the fusoid, yeast like or rod-shaped parasitic form of the fungus* cannot be found by microscopy Heavy sowings of pus or gumma material on glucose-agar or maltose-agar should yield characteristic glistening white, starfish-shaped colonies of the fungus after about 5 days incubation at 22 -24 C. If bacterial contaminants are present they may be suppressed by the enriching methods used in the isolation of ringworm fungi or by making transplants from the hyphal tips in the deep agar growth or by inoculating a male rat with the morbid material and isolating the fungus from the resulting testicular lesions.

Microscopically in microculture S schencki presents a slender branching, septate mycelium, about 2μ in diameter bearing, at first from the tips and later from the sides of hyphae and branches piriform, ovoid, or baton-shaped conidia, from 3 to 5μ in length arising from little denticles about 1μ high on the parent hypha. The colonies, at first glistening white, tend to become brown or blackish in aging. The species is pathogenic for albino rats, causing, especially a mycotic orchitis in which the parasitic form of the fungus is abundant.

The skin lesions of chromoblastomycosis have been classified by *Pardo-Castello Leon and Trespalacios (1942)* as (1) predominantly verrucose and papillomatous (2) tuberculoid or sarcoid (3) syphiloid, resembling gyrate subcutaneous gummata (4) psoriasiform and (5) an elephantiasic form resulting from cicatricial obstruction of the lymphatics. The cauliflower *like development* of the verrucose form giving the characteristic picture of mossy foot is strongly suggestive of the disease, although it may be mistaken for epithelioma, but the isolated, small papillomatous lesions, persisting with but little increase in size and no tendency to ulceration over periods of 8–12 years, may attract little attention and be dismissed as simple warts. In all its clinical forms, the diagnosis of this disease must rest upon the mycological examination, but, unlike the case of sporotrichosis, this is made more frequently by microscopy than by culture Histologically the lesion is primarily dermal with but little extension to the subcutaneous tissue. The cytological reaction is mainly reticulo-endothelial with infiltration of plasma cells, fibroblasts, usually some eosinophils, many multinucleate giant cells and aggregations *of polymorphonuclear leucocytes. The parasite, Phialophora verrucosa, P pedrosoi* or *P compacta* in the form of rounded, thick walled brown-coloured cells, 8–15μ in diameter sometimes septate but never budding, may be seen in

pairs or in small groups within the giant cells, in the polymorphonuclear cell masses or in other parts of the granuloma. These fungal cells, which may not be numerous, should be sought patiently. The epidermal reaction takes the form of marked acanthoses and hyperkeratosis with papilloma formation, and the different kinds of lesion seem to be determined by individual tissue responses in which an allergic element plays a part, rather than to differences in the infecting species, although Simson (1946), in an observation on 6 cases, noticed that the large solitary lesion on the one hand and multiple lesions on the other were associated with different varieties of *Phialophora pedrosoi*. The causative fungi are easily cultivated from the lesions, and in established infections antibodies against fungi of the group can be demonstrated in the blood.

Histoplasmosis, although essentially a systemic mycosis affecting the cells of the reticulo-endothelial system, frequently presents skin lesions which, in young infants, may be vesicular, pustular, crusted, scaly or purpuric, or in adults, papular, ulcerative, petechial or rarely bullous. In a unique, chronic case of histoplasmosis of more than 15 years' duration described by Hansmann and Schenken (1934), the skin lesions commenced as scaling patches on the popliteal spaces and eventually spread even to the scalp, eyebrows, palms, soles, and scrotum, so that no area of skin escaped involvement. The eruption, which was said to resemble dermatitis exfoliativa, consisted of closely-packed papules and macules measuring about 0.5–1.0 centimetre in diameter, irregular in outline and tending to become confluent. The summits of the papules were scaly and frequently showed superficial ulceration with many deeper ulcers measuring 3–4 centimetres in diameter. The whole skin was thickened, reddish-purple in colour and fissured in many places and there was intense pruritis. Histologically the papule, which was confined to the corium, consisted of a subepithelial granuloma of histiocyte cells filled with the parasite, with very little connective tissue reaction. A similar kind of case was identified in England in 1943 but the lesions were isolated and of annular shape resembling annular lupus, and the granuloma, which was confined to the corium, consisted of giant cells filled with an unusually large form of the parasite, measuring 12–15μ in the longer diameter instead of the common form from 3.5–4.0μ in diameter. The diagnosis of histoplasmosis is easily made by microscopical examination of smears or sections from the lesion, in which the fungus is seen as a small, thickly-capsulated oval yeast cell measuring 3.5–4.0μ in its longer diameter present in great numbers in the histiocytes and other phagocytic cells. The fungus stains well by Gram's method. Isolation of the fungus in culture from the pus or tissue of the lesion is not difficult, but the primary growth may take from 8 days to 3 weeks to appear. The best culture media to use are blood-agar for incubation at 37° C. upon which the yeast-like form of the fungus may develop, and the copper-tellurite-serum-agar medium of Allison and Ayling (1929) for incubation at room temperature, upon which the characteristic mycelial form will develop. Sowings should be heavy. Dermal sensitivity to histoplasmin may be demonstrated, but the specificity of the test awaits proof.

The skin lesions of coccidioidomycosis in the primary stage take the form of erythema nodosum which was present in 19 per cent of a series of cases described by Goldstein and Louie (1943). The nodules occur upon the tibial area, are transient, usually associated with rheumatic symptoms and are believed to be an allergic

manifestation Erythema multiforme, which is less frequent, occurs chiefly upon the upper limbs and the trunk. Diagnosis in the primary stage of the disease is based upon a history of possible exposure to infection and a positive coccidioidin skin reaction if the patient was known to have been insensitive previously Mycological diagnosis at this stage is difficult, but the thick walled, parasitic spherules of the fungus, measuring 10–80μ in diameter with many endospores, may be found in alkali treated sputum, or the fungus may be isolated in culture from the sputum, directly or by inoculation into mice. In the relatively rare coccidioidal granuloma stage, the skin lesions may be verrucose, developing from a small nodular papule to a plaque 2 inches in diameter Deeper nodules develop and, breaking down form indolent ulcers with papillomatous margins and a fungating character *often suggesting verrucose dermal tuberculosis. Circumscribed*, subcutaneous gummata or a diffuse subcutaneous infiltration forming the fixed tumour and subcutaneous cold abscess, which is sometimes connected with an underlying bony lesion are not uncommon The diagnosis in the granuloma stage is easily made by microscopy or culture In North American blastomycosis or Gilchrist s disease, although in a majority of cases, the infection is primarily pulmonary the skin lesions, primary or secondary are the most striking clinical feature. *The verrucose lesion which is the most characteristic of the disease*, usually consists of a painless crusted warty papule a few centimetres in diameter with prominent, raised, indurated, dark red margins and warty projections springing from the rather flattened surface, honeycombed by little sinuses from which the thick, glairy pus of micro-abscesses can be expressed. The ulcerating lesion is irregular in shape and frequently extensive, shallow or deep, with raised thickened margins, sometimes fungating, and a red granulating base discharging mucoid pus. *Other lesions* are the painless subcutaneous gumma and the cold abscess. The cutaneous lesions of the systemic disease are multiple but similar in character to *those of the purely cutaneous infection Histologically* the cutis shows a granulomatous infiltration with aggregations of polymorphonuclear cells forming microabscesses, and giant cells in which the parasite may be seen as a thick walled spherule 12–15μ in diameter in pairs or groups. The diagnosis is made by microscopy or culture. For culture, the pus or granuloma material should be heavily sown on blood-agar plates for incubation at 37° C.

The South American type of blastomycosis or paracoccidioidal granuloma was formerly confused with coccidioidomycosis, but is, *in fact, more closely related* to Gilchrist s disease. The initial lesion frequently occurs on the buccal mucosa or *adjacent mucosae as an ulcerating granuloma* from which the disease may spread by the lymphatics and become generalized Extension of the ulcerative process across the muco-cutaneous margin to the skin of the face, associated with the destructive submucous ulceration causes hideous deformity The skin lesion is formed of small, confluent violaceous papules which break down and form ulcers. A glandular form of the disease may closely simulate lymphadenoma. The diagnosis is made by culture or by the identification of *Paracoccidioides brasiliensis in the* often tuberculosis-like lesion in which it is seen as a thick walled spherule, 20–25μ in diameter frequently within giant cells, and sometimes showing a surrounding zone of smaller yeast-like cells resulting from multiple, simultaneous budding.

ALLERGY AND DERMAL HYPERSENSITIVITY

In the ringworm infections, dermal hypersensitivity to trichophytin like immunity depends upon infection of the skin by the living fungus. In experimental work on guinea-pigs it has been shown repeatedly that inoculation of living cultures into other tissues does not provoke dermal sensitivity unless the skin is also infected, nor will sensitivity result from injection into the skin of dead cultures or extracts such as trichophytin. The degree and, perhaps, the quality of sensitivity depends upon the infecting species, and is much greater with *Trichophyton mentagrophytes T. quinckeanum*, and *Microsporum canis*, all of which are parasites of the lower animals but capable of causing inflammatory lesions on man, than with *Microsporum audouini Trichophyton tonsurans* or *T. schönleinii*, which are essentially parasites of man and are well adapted to this host. Jadassohn, Schaaf and Wohler (1937) using the Schultz Dale experiment with the artificially sensitized uterus of the guinea-pig and a qualitative desensitization technique, demonstrated that various trichophytins contained a predominant, dermatophyte group allergen and other allergens associated with hyphomycetes in general or derived from the culture medium, but there were also some more specific elements. The trichophytin reaction may be accepted as a *group test* which is a measure of the state of dermal allergy great in certain infections and absent in others. It cannot, therefore, form the sole basis of diagnosis, but it is a useful ancillary test, especially when, as in suspected mycid eruptions, it is necessary to determine if a state of pronounced skin sensitivity exists. Mycids, or more specifically trichophytids, on the hands in cases of tinea pedis may take the form of cheiropompholyx, but fungal allergy is not the most frequent cause of this vesicular condition, and Davidson and Birt (1943), dealing with 200 cases of vesicular eruptions on the hands, attributed 75 per cent to dermatitis venenata. Of the remainder about one-half presented the cheiropompholyx character but only one-third of these were mycids. Benedek *et al.* (1943), in a study of 983 cases of cheiropompholyx, found clinically active lesions of the feet in only 1·9 per cent and all were mycologically negative.

In some of the systemic mycoses, e.g. coccidioidomycosis, dermal hypersensitivity to the specific and related allergens may persist for a very long time after recovery from the active disease, so the dermal reaction has little value in diagnosis unless it can be shown from the results of previous tests, that the state of dermal hypersensitivity is of very recent development. In the systemic mycoses the test finds its greatest usefulness in epidemiological surveys, and the recent great development in the knowledge of coccidioidomycosis owes much to the preliminary mapping of endemic areas on the results of the coccidioidin test. A similar survey using the histoplasmin test, is being used in an attempt to elucidate the epidemiology of histoplasmosis. Probably none of the dermal reactions to fungal allergens is strictly specific coccidioidin seems to have given the most specific results in practice but *Coccidioides immitis* may be a *Phycomycete* and therefore unrelated to the great majority of other pathogenic fungi. It is antigenically linked to *Haplosporangium parvum*, as demonstrated by Emmons, Olson, and Eldridge (1945) who have also shown that histoplasmin and blastomycin give cross-reactions. In diagnostic dermal sensitivity tests a negative result may be

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valuable if it indicates absence of infection but it may be due to a pre allergic stage of the disease or to a state of anergy resulting from an overwhelming infection. In blastomycosis, a state of allergy is a contra-indication to iodide treatment and blastomycin is used not only to detect the allergic state but to bring about desensitization before the introduction of the drug treatment.

Immunity to fungal infections

Amongst the dermatophytes, the well-adapted, host specific parasites tend to infect only the young of the host species, and the infection disappears spontaneously at puberty That the specific post pubertal immunity is related to the maturation of the reproductive organs seems probable, but experimental treatment of young children, infected by *M audouini* with sex hormones, by Lewis and Hopper (1937) was not successful

Acquired immunity against ringworm, as a result of infection, is variable in degree and duration and concurrent or consecutive infections by different species of dermatophytes are not infrequent. Experimentally as shown by Catanei (1945) and others, the cuti resistance following infection of the skin of the guinea-pig is of relatively short duration and often incomplete and it is usually marked by a state of dermal hypersensitivity to trichophytin The whole question of infection-resistance and acquired immunity to re-infection especially in the case of tinea pedis calls for fuller investigation

Little is known of immunity in the systemic mycoses, but antibodies may be demonstrated in the blood in coccidioidomycosis, blastomycosis, sporotrichosis, chromoblastomycosis, moniliasis, and other mycoses, especially when the disease is progressive—in fact, in coccidioidomycosis a progressively rising titre of serum antibody is accepted as a bad prognostic sign. On the other hand, Smith *et al* (1946) have noticed that persons reacting positively to the coccidioidin skin test, and therefore showing evidence of previous coccidioidomycosis, did not contract the clinical disease when exposed to infection.

Treatment and prognosis

With a few exceptions chemotherapy has proved very disappointing in the systemic mycoses Potassium iodide pushed almost to the limit of tolerance and continued over a relatively long period is frequently effective in actinomycosis, is a specific in the superficial uncomplicated forms of sporotrichosis, and has proved useful in the purely dermal form of blastomycosis (Gilchrist s disease) in which, however it must be used with caution The sulphonamides and penicillin are effective only in actinomycosis. No kind of drug treatment has been found effective in histoplasmosis, coccidioidal granuloma intracranial torulosis and the visceral forms of blastomycosis, paracoccidioidal granuloma and even sporotrichosis, and the prognosis in these diseases is bad. Localized disease, such as chromoblastomycosis, may be dealt with by surgical excision or x-ray therapy Rest with dietetic and symptomatic treatments has proved of value in primary coccidioidomycosis, as it has in tuberculosis Specific therapy has been used with some success mainly as an ancillary treatment and this field might be more fully developed but in the therapy of systemic mycoses the example of the analogous disease tuberculosis, must be kept constantly in view

CHAPTER 11

PSYCHOLOGICAL ASPECTS OF DERMATOLOGY

E. Wittkower

Attempts at introducing psychological concepts into dermatology in the past have not been too successful. The reasons for this failure seem to be obvious. Dermatologists know too little about psychological medicine, and medical psychologists too little about dermatology. In any case, articles on dermatological subjects by the latter were often much too technical and did not carry much weight with the former. Moreover, to a certain extent there seems to be an antithesis between dermatology and psychological medicine. Dermatologists, in view of the nature of their speciality, focus their attention on the body surface, whereas psychological problems do not lend themselves to visual conception. The credit goes to Klauder (1925), O'Donovan (1927), Barber (1930), Sack (1933), Stokes (1935), Gillespie (1938), Klaber and Wittkower (1939), Ingram (1939), Becker and Obermayer (1940), and MacKenna (1944) for stressing the importance of psychological factors in dermatology and for trying to bring about a synthesis of both branches of medicine.

Review of recent work

Impetus was given to interest in the psychological aspects of skin disease through the independent studies of Stokes (1935) and Rogerson (1937) concerning the eczema-asthma-hayfever or asthma-prurigo personality. According to both writers, patients suffering from these conditions are characterized by feelings of insecurity and of inferiority, by over-dependent and narcissistic trends combined with a tremendous drive, restlessness, over-ambitiousness and an "all-or none" type of reactivity which Stokes named the tension frame of mind.

A different line of approach was attempted by Becker and Obermayer (1940), who, by means of social and functional studies, tried to assess the relevance of adverse social factors and of what they call neurocirculatory instability for the aetiology of dermatoses. They class as neurodermatoses: generalized and localized idiopathic pruritus, neurotic excoriations, neurodermatitis (both dry and exudative types), dyshidrosis, idiopathic chronic urticaria, angioneurotic oedema, alopecia areata, lichen planus, vitiligo, and rosacea. Other dermatoses which, in their view, possibly belong in this group are dermatitis herpetiformis, chronic idiopathic erythema multiforme, stomatitis aphthosa, and ulcus neuroticum oris.

Heller (1944), starting from L. Brocq's division of skin conditions into two groups—skin diseases proper and skin reactions—pointed out that skin reactions depend for their characteristic type—urticarial, eczematous, psoriasiform—upon the make-up of the patient rather than on the specificity of any external factor which may be involved. He believed that the hypersensitivity of the skin of eczema patients, for instance, was only one aspect of a generally hypersensitive make-up.

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CHAPTER 11

PSYCHOLOGICAL ASPECTS OF DERMATOLOGY

E. WITTKOWER

ATTEMPTS at introducing psychological concepts into dermatology in the past have not been too successful. The reasons for this failure seem to be obvious. Dermatologists know too little about psychological medicine, and medical psychologists too little about dermatology. In any case, articles on dermatological subjects by the latter were often much too technical and did not carry much weight with the former. Moreover, to a certain extent there seems to be an antithesis between dermatology and psychological medicine. Dermatologists, in view of the nature of their speciality, focus their attention on the body surface, whereas psychological problems do not lend themselves to visual conception. The credit goes to Klauder (1925), O'Donovan (1927), Barber (1930), Sack (1933), Stokes (1935), Gillespie (1938), Klaber and Wittkower (1939), Ingram (1939), Becker and Obermayer (1940), and MacKenna (1944) for stressing the importance of psychological factors in dermatology and for trying to bring about a synthesis of both branches of medicine.

Review of recent work

Impetus was given to interest in the psychological aspects of skin disease through the independent studies of Stokes (1935) and Rogerson (1937) concerning the eczema-asthma-hayfever or asthma-prurigo personality. According to both writers, patients suffering from these conditions are characterized by feelings of insecurity and of inferiority, by over-dependent and narcissistic trends combined with a tremendous drive, restlessness, over-ambitiousness and an "all-or-none" type of reactivity which Stokes named the tension frame of mind.

A different line of approach was attempted by Becker and Obermayer (1940), who, by means of social and functional studies, tried to assess the relevance of adverse social factors and of what they call neurocirculatory instability for the aetiology of dermatoses. They class as neurodermatoses generalized and localized idiopathic pruritus, neurotic excoriations, neurodermatitis (both dry and exudative types), dyshidrosis, idiopathic chronic urticaria, angioneurotic oedema, alopecia areata, lichen planus, vitiligo, and rosacea. Other dermatoses which, in their view possibly belong to this group are dermatitis herpetiformis, chronic idiopathic erythema multiforme, stomatitis aphthosa, and ulcus neuroticum oris.

Hellier (1944), starting from L. Brocq's division of skin conditions into two groups—skin diseases proper and skin reactions—pointed out that skin reactions depend for their characteristic type—urticarial, eczematous, psoriasiform—upon the make-up of the patient rather than on the specificity of any external factor which may be involved. He believed that the hypersensitivity of the skin of eczema patients, for instance, was only one aspect of a generally hypersensitive make-up.

The first attempt at co-ordinating skin conditions and personality types was undertaken by MacKenna (1944) Elaborating a suggestion made by Hodgson, MacKenna classified skin conditions according to the personality types to which they seem to be related He differentiated five personality types low intelligence, hysterical narcissistic grossly anxious and obsessional (*see below*).

In a still more recent article Hodgson (1945) contrasted two clinical groups of psychosomatic skin diseases—frictional and spontaneous—and submitted the view that in individuals with neurocirculatory instability friction leads to excoriation, eczematization and lichenification according to the basic skin type of the integument involved He classified the basic skin types as being normal, ichthyotic, seborrhoeic and eczematous. In his view examples of spontaneous diseases are acute exudative neurodermatitis and acute erythemata (in normal types of skin) exacerbations of eczematous changes (in ichthyotic skins) exacerbations of the respective conditions (in seborrhoeic and eczematous persons).

Psychological aspects of dermatology in general

The above review of the recent literature shows that our knowledge about the psychological aspects of skin diseases is still very rudimentary and that systematization is still lacking. To obtain the right perspective it is necessary to discuss some modern psychiatric concepts and to apply them to dermatology in general before dealing with specific syndromes

Some psychiatric considerations

Psychosomatic medicine has been defined as a proportionate assessment of psychological and physical factors in medicine In this wide sense there is hardly any disease in which psychological factors do not play a part, aetiologically or as far as the individual reaction to the disease is concerned. In a narrow sense psychosomatic medicine concerns itself with those disorders of which the direct and immediate aetiology is attributable to emotional factors.

Psychosomatic disorders are disorders of the emotionally maladjusted, but not every emotionally maladjusted individual develops a psychosomatic disorder A constellation of hereditary and acquired physical and mental factors is necessary to produce the malady and, in this connexion, the following points may be noted

(1) *Heredity*

True inheritance of disease is rare. More commonly predisposition to disease is inherited or apparent heredity is simulated by the unconscious identification of an individual with a previous sufferer from the same disease in the family

(2) *Acquired features*

Acquired weak spots such as those caused by scalding and fractures may determine the site of a psychosomatic affection but not the affection itself

(3) *Previous personality*

Psychologically personalities prone to develop psychosomatic disorders are either psychiatrically ill or suffer from character disorders. In the former psychiatric illness is transformed into physical illness, in the latter a psychosomatic disorder develops as a substitute for a frank nervous breakdown A character disorder is to a neurosis what a compensated valvular disease is to a decompensated valvular disease thus patients suffering from character disorders may be unaware

of any psychological difficulties and yet, on expert examination—and often not only on expert examination—they may exhibit anomalies in thought, feeling, and action.

CLASSIFICATION OF CHARACTER DISORDERS

Various classifications of character disorders have been suggested. For practical purposes a classification into obsessional and hysterical characters is as good as any. The differences between the two character types are contrasted in Chart I.

CHART I. CLASSIFICATION OF CHARACTER DISORDERS

	Obsessional	Hysterical
1. Background and early history	Hard-working, fussy nagging, stern parents	Youngest of the family: only child, spoilt
2. On examination	Quiet, serious, accurate, formal	Affected in manners and speech, emotionally immature, dramatic, self-pitying
3. Emotional life	Bottle up emotions	Emotions freely displayed, but shallow. Act on impulse rather than on logical reasoning. Sentimental, over-enthusiastic, dreamy imaginative: use imagination for self-aggrandisement
4. *Self-esteem*	Uncertain of themselves: feelings of inferiority, of inadequacy, of incompetence	Vain and conceited in childish way
5. Social behaviour	Retiring, shy in social contacts, especially in the presence of persons in authority, of strangers, of members of the opposite sex	Seek and enjoy social intercourse. Tend to dominate the stage
6. Affection	Loyal	Much too fond of themselves to be really fond of anybody else: over-dependent
7. *Sexuality*	Inhibited. Severe morality be- sexual trends	Philandering
8. *Aggressiveness*	Afraid of hurting other people. Obstinate, pigheaded, resentful of interference from above	Afraid of getting hurt, self-pitying
9. *Drive*	Work hard, over-conscientious, methodical, meticulous, pedantic, persevering, tend to doubt and to check: indecisive, slow: worry unduly	Lack perseverance: do not care: lazy: resent demands made on them, and discomforts
10. At leisure	Tense, rigid, cannot relax, sleepless	Can relax, pleasure-seeking
11. *Cleanliness*	Overclean, overtidy	Unconcerned
12. *Financial security*	Parsimonious, over-concerned about financial security	Unconcerned, extravagant, selfish
13. Symptoms	Morbid fears and doubts: compulsive actions	Trembling, crying, aches and pains, bedwetting

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The italicized features of *the chart demonstrate focal points* at which individuals subject to psychosomatic disorders, break down when they do break down. Generally speaking, our mode of behaviour and our predictable reaction to any given situation depend upon focal conflicts in the structure of our character. As regards psychosomatic disease, it has been shown on examination of large numbers of patients *suffering from the same disorder that there is a surprising* uniformity in the area of their focal conflicts. Thus patients with hypertension have in common conflicts over aggressiveness those suffering from night-blindness—conflicts over dependence, and women with dysmenorrhoea—conflicts concerning bisexual trends. Persons suffering from peptic ulceration are primarily concerned with bread *and butter problems but those who have colitis*—whilst they may comply with the dictates of cleanliness, may be in rebellion against them. But even in the area of focal conflicts there are variations which determine the choice of symptom.

Any additional load on the already heavily burdened emotional conflict situa*tion may precipitate the onset of a pyschosomatic disorder. It is a common mis*take to attribute psychosomatic disorders and for that matter psychological disorders in general to current difficulties, whereas, in fact current difficulties only intensify already existing emotional difficulties until a breaking-point is reached.

The symptoms which develop depend on three factors (1) the nature of the focal conflict, (2) hereditary predisposition and (3) the psychological meaning of the symptoms. Every psychosomatic symptom serves a definite purpose, which is more easily recognizable in hysterical characters than in obsessional characters. The formation of the psychosomatic symptom represents an incomplete and, from the viewpoint of the patient an unsatisfactory solution of his emotional problem. By producing *his symptom the patient presents his emotional conflict* and makes unconsciously a decision which consciously he may be unable to accept.

PSYCHIATRIC CONSIDERATIONS APPLIED TO DERMATOLOGY

Psychosomatic skin disorders do not differ from other psychosomatic disorders as far as general criteria are concerned. The only difference arises from the fact that it is the skin which is affected and the questions to be answered are first, why the skin is affected, and secondly why it is affected in the way it is.

(1) Heredity

It is conceivable that different individuals are constitutionally endowed with different types of skin that some individuals on constitutional grounds make use of their skins as a medium for emotional expression more readily than others, and that their basic skin types, on the lines of Hodgson's conception determine the nature of the skin affection displayed. From the holistic point of view however it is more likely that the skin fits its owner and that certain skin types are related to certain personality types.

There is evidence *that the predisposition to specific skin disorders* is hereditary. Emotional factors bring to light predispositions which otherwise might remain dormant, determine the time of onset of the eruption and maintain it or precipitate relapses.

(2) Previous personality

Other skin diseases seem to be personality-bound. MacKenna (1944) has suggested that dermatitis artefacta is associated with an hysterical personality whereas neurodermatitis, seborrhoeic dermatitis, prurigo simplex, and pruritus ani et vulvae are disorders frequently encountered in obsessional subjects patients suffering from rosacea, pompholyx, hyperidrosis, *acne excoriée des jeunes filles* have been found to be of an anxious temperament. Exudative dermatoses often occur in narcissistic individuals, and skin infestations are common in persons of low intelligence. In any case, as MacKenna has pointed out, the reaction of individuals to their skin affections, whatever the aetiology of these maladies may be, is bound to be influenced by the person s make-up. *Obsessionals, for instance,* if they develop scabies are driven mad with itching —by the very idea of being infested.

(3) Focal points

Fruitful though it is, the personality approach to skin disease labours under the handicap of assigning a large variety of skin diseases to a small number of personality type categories the approach also fails to encompass the important relationship between personality features and actual symptoms displayed. This handicap can be overcome by breaking up personality types into traits and by arranging skin phenomena according to the focal points and focal conflicts to which they appertain.

Four focal points, in particular have an immediate bearing on the skin self esteem, sexuality aggressiveness, and cleanliness.

(*a*) *Self-esteem*

The skin and its appendages, in beauty and the beast, are used as means of attraction in humans they also serve for self-display and self-decoration. Individuals who are shy are apt to blush. This blush of modesty is due to a conflict between the desires of making oneself conspicuous and of hiding oneself in the darkest corner possible. It is a result of a compromise just as a well-tailored evening frock covers and exhibits the shapely form of its wearer so blushing, though indicative of modesty is considered as attractive and, in fact, invites the attention of the observer

(*b*) *Sexuality*

Similarly the blush of innocence is incompatible with true innocence. A girl who blushes on hearing a risqué story reveals, by blushing, that she has understood the joke but that her morality does not allow her to enjoy it. Like the blush of modesty the blush of innocence is a compromise between two conflicting trends. Psychologically it is a displacement upward.

On a perceptory level the skin conveys affection, tenderness, and sexual stimulation—some areas more than others. By means of repressive forces an individual may divorce skin sensations from their emotional and sensual content. Thus an individual may genuinely and almost naively profess that he is unaware of the pleasurable sensation which he derives from scratching himself

(*c*) *Aggressiveness*

Scratching is an aggressive act it also serves the removal of something unpleasant and disturbing which *may* be present in reality in phantasy or in a figurative sense A person for instance who has to cope with a tricky task may scratch his head *in lieu of the task* which bothers him and which he wants to be removed. There are several psychological components in the act just described a transient sense of *frustration* which rouses aggressiveness, repression of hostile impulses, and shifting of *aggression* from one object to another In other words, aggressiveness deprived of an external outlet by an authority within the individual may become self-directed and turned towards the easily accessible skin

(*d*) *Cleanliness*

Cleanliness is an acquired characteristic babies and small children do not mind being dirty and even seem to enjoy it. Pleasure in being dirty not infrequently persists into adult life—though usually completely unrecognized by the persons concerned—in the inverted form of fastidiousness and of over-insistence on cleanliness The words dirt and dirty are used in a literal and in a metaphorical sense Impurity of the skin, in popular belief is attributed to dirty habits *in the double meaning of the words* people often believe that it is written on a person s face whether he has trespassed upon the accepted moral code. Hence *individuals* who feel unclean irrespective of whether they are or not, are ill at ease they often experience an itching sensation and an urge to scratch themselves. Feelings of uncleanliness are frequently related to feelings of guilt.

(4) Focal conflicts

What is true for the little conflicts of everyday life is equally true, and even more so for the major conflicts of persons suffering from character disorders. Intensification of their conflicts over self-esteem, sexuality aggressiveness, and cleanliness leads to an intensification of corresponding emotional states and skin reactions it also causes anxiety which by itself as in the case of hyperidrosis, or in conjunction with other emotions stimulates skin activity A disturbing environmental event (current conflict) ignites the fuse which leads to the explosive store of deep-seated emotions (focal conflicts). The explosion or even the smouldering of these conflicts, brings about specific emotional states which set into motion specific and corresponding skin mechanisms. Originally functional skin alterations may afterwards become structuralized.

CHART II. FOCAL CONFLICTS

Conflicts concerning		Physiological responses	Pathological responses	Examples
Self-esteem –	–	Blushing Perspiring	Spontaneous disease	Seborrhoeic dermatitis Sycosis Rosacea, acne vulgaris
Sexuality –	–	Sebum production		Pruritus vulvae Pruritus ani
Aggressiveness	–	Flushing Scratching	Frictional disease	Prurigo simplex Neurodermatitis
Cleanliness –	–	Itching Scratching		

Chart II is an attempt at relating focal conflicts which have a bearing on the skin to their physiological and pathological responses. The chart shows that spontaneous skin diseases are predominantly related to conflicts over self-esteem and sexuality and fictional diseases to conflicts over aggressiveness and cleanliness. It must be borne in mind, however that a tabulation of this kind is always an over-simplification of a complex problem and that overlaps between the groups are unavoidable.

(5) Psychological meaning of symptoms

Psychologically the skin serves as a barrier between a person's inner world and the outer world. Owing to this peculiar position, psychosomatic skin disorders almost invariably affect, and are affected by both. A skin disorder may be *guilt motivated* (as are many cases of rosacea, seborrhoeic, and eczematoid dermatitis), and its only subjective references to the outer world may be the sufferer's urge to confess his guilt and the self punishing disfiguring effect of the complaint, or the patient may be blissfully unaware of any emotional conflict and yet the development of the skin disorder may serve all too obviously the personal advantage of its sufferer as in many cases of pompholyx (Chart III). One may quote for example the case of a girl who, to oblige her sadistic partner produced urticarial weals at the site of his whippings without having to endure the painful procedure of being whipped and the case of the husband who toying with the idea of infidelity developed an angioneurotic oedema on his ring finger on the day of his wife's departure for a holiday

CHART III. PSYCHOLOGICAL MEANING OF SYMPTOMS

Psychological factor	Emotional state	Psychological meaning of symptom	Examples
Emotional	Feelings of guilt	Urge to confess Self-punishment	Rosacea Seborrhoeic dermatitis Eczematoid dermatitis
Conflict	Emotional dissociation *Belle indifference*	Plea for sympathy Evasion of unpleasant situation	Dermatitis artefacta Pompholyx

In terms of body language—eloquent for those who understand it—psychosomatic skin disorders often reveal some of the sufferer's emotional conflicts permanent recovery can be ensured only by the solution of these conflicts.

(6) The psychodynamics of skin disease

The psychodynamics of skin disease can therefore be conceived and summed up as follows. Individuals who may or may not be constitutionally predisposed to skin disease and who are predisposed to emotional conflicts, especially in the spheres of self-esteem, sexuality aggressiveness, and cleanliness, are exposed, or expose themselves, to situations which intensify these conflicts. Intensification of these conflicts either causes anxiety feelings of guilt, an urge to confess and a

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Aggressiveness –	– Flushing Scratching	Frictional disease	Prurigo simplex
Cleanliness –	– Itching Scratching		Neurodermatitis

loyalty Owing to their highly developed sense of responsibility seborrhoeic patients tend to postpone matrimony until they are rather advanced in years their sense of obligation makes them considerate husbands, very much concerned about the well-being and especially the financial security of their families.

Their main conflict arises from their repressed aggressiveness and shows itself predominantly in their anxiety in social contacts. They are over-anxious to be on good terms with their fellow beings because they are unable to tolerate hostility actively and passively and because they are constantly afraid that their own hidden aggressiveness may be found out. They need plenty of goodwill as a means of self-assurance that this has not been the case yet, and they tend to expect the worst because, unrecognized by themselves, they believe that they do not deserve any better

Almost without exception, incidents leading up to the onset of seborrhoeic dermatitis either affect the patients social status or their self-esteem Both of them are closely interrelated. Individuals delicately poised in their self-esteem are obviously apt to react severely to any threat to, or to any actual lowering of their social status and, conversely any additional burden to a self-esteem already overladen with feelings of guilt, is likely to lower the individual, in his opinion, in the eyes of the world. It looks as if the seborrhoeic patient does not only feel ostracized because of his skin affection, but that he is prone to develop the eruption because he feels and believes he has reason to be ostracized.

Acne vulgaris

Popular belief has it that there is something wrong with the sex life of a youth whose face is covered with pimples. As will be seen, popular belief is not far off the mark.

The typical acne patient is diffident on examination and is quiet and well mannered there may be something furtive about his or her appearance.

These individuals often grow up in a repressive, puritanical, Victorian atmosphere frequently they describe their parents as hard working and devout Christians, and say that swearing was forbidden at home. As children the patients were usually well-behaved or if they were troublesome, their aggressiveness has been knocked out of them long ago. Sometimes they are aware of feelings of hostility against their stern and austere parents, but more often than not they bear no malice. Sexual matters have never been mentioned at home or have been treated in the traditional hush-hush manner

Their puberty has been stormy—but not on the surface. For instance, check against restricting authority so common in early adolescence, has usually been absent.

Girls, more often than is usual, resent their menstrual periods as messy

Superficially acne patients are models of virtue. They are serious in their approach to life and often devoid of sense of humour It is rather difficult to make an acne patient smile. They work hard, are eager to please their superiors and to get on in the world. To do this they are prepared to sacrifice a good deal of their spare time. Classical music and good books appeal to them rather than jazz,

desire for self-punishment or it leads to emotional dissociation and flight into illness with display of *belle indifference* On both occasions skin mechanisms, or mechanisms related to the skin come into operation these mechanisms are similar to the blush of modesty the blush of innocence, and the flush of rage, or to the itching of a person who feels unclean, or the scratching of a person who is confronted by a difficult task

SPECIFIC SYNDROMES

In the light of our present knowledge no single person is in a position to cover the special psychopathology of psychosomatic skin disorders from his own experience Even to draw on the available literature is of little help because the investigations which have been reported have been carried out at different levels ranging from superficial inquiries into current worries to the penetrating scrutiny of psychoanalytical research. Anybody who would try to put the disconnected pieces together would therefore find himself in a position similar to that of a geologist who tries to make out a geological structure on the basis of specimens obtained by different workers from different strata and in different areas. For this reason the following discussion is based mainly upon the writer s own observations.

Seborrhoeic dermatitis

Seborrhoeic patients, because they are not easy talkers, are not very easily accessible to psychiatric approach Once their protective armour has been pierced they become co-operative but even then they usually maintain a respectful aloofness. Their hands are often clammy and they blush easily

More than half the number of the seborrhoeic patients' studied, according to their accounts, had been spoilt or ill-treated as children or had grown up in an insecure environment Whether they had been spoilt or ill-treated they always longed for love and still more love. Some of them felt unwanted. Perhaps they were unwanted and unpopular at home because people are apt to sense sullenness and vindictiveness lurking behind a docile façade.

Their school and work records were, and are, usually favourable almost without exception they are conscientious, painstaking workers. If they have nothing to do they feel bored and tense, and become restless. Rules and regulations are their hearts delight and everything is carried out to the letter Whatever they do, they want to do as perfectly as possible. They are sticklers for punctuality and orderliness and expect the same from others. Their desire to work hard and their perfectionistic trends are prompted by feelings of inadequacy and of inferiority and by fears of insecurity and of punishment. They require praise and encouragement to stabilize their self-confidence, at least for the time being but adverse criticism disheartens them and threats frighten them to a disproportionate extent. Seborrhoeic patients are usually shy reserved and retiring or less commonly of a solitary nature. Some of them keep away from crowds and social activities altogether others, who go to parties, enjoy themselves quietly as spectators rather than as participants. Very few of them go to dances, for fear of making themselves conspicuous, and especially of being laughed at, keeps them off the floor Usually they are slow in making friends, but once they have made them they stick to them

if addressed, become embarrassed or tongue-tied. They not only blush, but may stammer or tremble. Like acne patients, they are usually inhibited and often harassed by conflicts over immature sexuality

The main differences between rosacea and acne vulgaris arise from the facts that rosacea usually starts much later in life than acne vulgaris, that anomalies of behaviour in rosacea patients are much more striking and, therefore, hit the eye very forcibly and that, in contrast to seborrhoeic dermatitis and acne, rosacea patients are frankly and consciously preoccupied by feelings of guilt and shame which erroneously they attribute entirely to current situations. Their willingness to disclose minor or major delinquencies amounts, in some cases, to a compulsive urge to confession, and clearly represents an attempt at relieving severe internal tension

As might be expected, disturbing events preceding the onset of rosacea are usually related to problems of social contacts and of sexuality

Pompholyx

More often than can be due to chance, pompholyx occurs in individuals who are emotionally maladjusted. Before the onset of their complaint a majority of them display features described above as typical of the hysterical or of the obsessional character but without predominance of the one or of the other In particular excessive self-love (narcissism) is very common this may show itself in the form of childish vanity or as a morbid fear of getting hurt, in hysterics, or in the form of overweening ambition as an abnormal fear of failure or of showing fear in obsessional subjects. A history of psychosomatic affections, pre-existing to or co-existing with the skin complaint, can frequently be obtained thus complaints are often made of intractable headaches, fainting fits, cardiac pain nervous dyspepsia, and of bedwetting (in adult life).

Disturbing events leading to the onset of the pompholyx eruptions are frequently of such a nature as to hit the patients where it hurts them most. They consist of blows to their vanity frustration of their ambitions, actual failures, and exposures to dangers and hardships. Varying to some extent as to whether the hands or the feet are affected and equivalent to an hysterical episode, the development of pompholyx seems to serve a definite purpose. In terms of body language, it seems to convey that an individual wishes to throw in his hand or is unwilling to use his feet or in a sub-group of those in whom the onset of the skin complaint coincides with a break-through of hidden impulses, it seems to represent an urge to confess and to atone.

Psoriasis

In a different way emotional factors enter into the aetiology and course of psoriasis.

Psoriasis is not bound to any one personality type, either physically or mentally In a series studied, the range of personality types covered people as diverse as a burglar at one end of the scale and law-abiding, God-fearing citizens at the other In some cases the psoriasis started in early childhood. Of those whose personality could be made out with reasonable accuracy 60 per cent were

thrillers, and cheap love stories If they have got the educational background, their minds may be preoccupied with the depraved state of the world and with world reformatory ideas. Often they are deeply religious and disdainful of the minor indulgences of life, which they regard as frivolous. Their views are often rigid, dogmatic, and intolerant. Everything has to be right, just right, and nothing but right and if they do not come up to these standards they are unduly worried.

Closer examination reveals that they are stunted or at least retarded, in their emotional growth Because they are inoffensive they are usually easy to get on with but behind a meek façade they harbour aggressive phantasies and impulses whose concealment, to a certain extent accounts for their difficulties in social contacts Apparently helpless, they ask anybody and everybody for advice and afterwards do what they think fit passive resistance, resentment of authority and rigidity of outlook are other forms of displaying their hidden aggressiveness. Socially they had been anxious and shy long before the onset of their skin trouble. Usually they hate parties, crowds, and noise, and the idea of making themselves conspicuous, or of being held up to ridicule, frightens them. In particular they feel ill at ease in the presence of members of the opposite sex this, of course, is very common in boys and girls during puberty but in acne patients it persists almost indefinitely Hardly any one of those studied had other than platonic friendships they were prevented from going any further by their severe morality Without being questioned, most of them expressed themselves very strongly—and unusually strongly—in their condemnation of masturbation, premarital intercourse, extramarital infidelity and divorce. Very few of them practised masturbation and if they did they felt unusually guilty about it.

Emphasis on their moral restraint indicates a struggle within themselves between a desire for sexual expression and prohibiting forces, resulting in severe feelings of guilt. It is conceivable that this internal conflict forms the background of their skin affection

Rosacea

A typical rosacea patient, a woman in her thirties, neatly but unassumingly dressed appears shy and reserved at the beginning of the interview She is apprehensive, suspicious of what is going to occur and reluctant to speak. She sits on the edge of the chair clutching her handbag tightly or fidgeting with it. At the first question to which she attaches importance a flush appears on her cheeks. Repeatedly she interrupts her account to ask if she is not causing too much trouble, or if she is not being silly Gradually as confidence is gained, she expands and, eventually often in a flood of tears, she pours out some incident to which she attributes the onset of her complaint.

As may be gathered from this description rosacea patients have much in common in their personalities with patients suffering from seborrhoeic dermatitis and acne vulgaris. Like seborrhoeic patients, and for similar reasons, they are anxious in their social contacts For days or weeks before a social engagement they feel worried and uneasy Entering a room containing unfamiliar faces represents a major ordeal for them They like to be in the background, to fade away and shrink into themselves They have difficulty in entering into conversation and,

if addressed, become embarrassed or tongue-tied. They not only blush, but may stammer or tremble. Like acne patients, they are usually inhibited and often harassed by conflicts over immature sexuality

The main differences between rosacea and acne vulgaris arise from the facts that rosacea usually starts much later in life than acne vulgaris, that anomalies of behaviour in rosacea patients are much more striking and, therefore, hit the eye very forcibly and that, in contrast to seborrhoeic dermatitis and acne, rosacea patients are frankly and consciously preoccupied by feelings of guilt and shame which erroneously they attribute entirely to current situations. Their willingness to disclose minor or major delinquencies amounts, in some cases, to a compulsive urge to confession, and clearly represents an attempt at relieving severe internal tension.

As might be expected, disturbing events preceding the onset of rosacea are usually related to problems of social contacts and of sexuality

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emotionally maladjusted a percentage far in excess of a cross-section of the population. However there was neither a uniformity in the type of maladjustment nor in basic conflicts One in two of those whose psoriasis started in early childhood, one in three of those who were emotionally well-adjusted but only one in six of those who were emotionally maladjusted reported that other members of their families suffered from the same malady

These observations seem to suggest that individuals in whom the hereditary element is very powerful may develop psoriasis in any case, whereas others need a catalyst to mobilize a dormant predisposition to psoriasis. Emotional crises of a nature specific to the individual affected but varying in nature, often seem to assume this function In other words, if an individual is emotionally maladjusted for reasons unrelated to psoriasis, the emotional maladjustment may but need not, take charge of the psoriasis, and determine its onset, persistence and relapses.

ILLUSTRATIONS

The following examples illustrate the syndromes described

Seborrhoeic dermatitis

A warrant officer aged 30 had struggled against adversity throughout his life. His parents were very poor not enough money was available to feed seven hungry mouths. Before the war after a hard uphill struggle, he had established himself in a fairly secure position as a wireman in an engineering depot.

He was a man of few words and of few friends Though he was successful in the Army he had never been certain of himself He had always worried a great deal and problems of responsibility and of security especially had always been very much on his mind

In 1941 his wife was living in Wales the landlord wanted to evict the woman so that he could sell the premises The patient obtained leave to find another home but failed. On return to his unit he had his first attack of seborrhoeic dermatitis.

In 1942 his wife was pregnant. During her pregnancy she became very seriously ill Removal of the child was deemed necessary He developed a second attack of seborrhoeic dermatitis.

In 1944 he was in the bridge head in Normandy This was his first time in action The job of a gun position officer was entrusted to him. There is a terrible lot of responsibility to it he said, if you ve got a gun wrong you get a lot of your men killed After a fortnight he had to be withdrawn from the line because of a third attack of seborrhoeic dermatitis.

At Christmas 1944 he went on leave and found that his wife had spent money which he had asked her to save, on drink. They had a serious row over it, and when he returned to his unit he had his fourth attack of seborrhoeic dermatitis.

Acne vulgaris

A guardsman aged 20 had been brought up in a repressive atmosphere. His father a wealthy merchant, had been in poor health for several years, but he is the type of man who keeps going uncomplainingly even if it kills him in the end

The patient himself had always been shy and retiring. The very idea of mixing with the common crowd was abhorrent to him. He enjoyed a serious discussion with some congenial male friends, but felt embarrassment and did not know what to say in the company of girls. Duty first had always been his principle. In fact, he took his duties so seriously that, worrying about them, he had had many sleepless nights. He took a poor view of the artificial pleasures of many of his contemporaries. He had never been to a dance and disapproved of dancing. Tolstoy was his favourite writer. He was seriously concerned about the state of world affairs and foresaw a major catastrophe in the not too distant future. He attributed all evil in this world to modern scientific discoveries, and would like the world to go back to the halcyon days of one hundred or two hundred years ago.

Before he joined up he was secretary of a Youth Organization whose ideals he still tried to uphold. His views on morality were very rigid. Sexual matters are a silly thing and I disagree with them entirely he said. He strongly condemned extramarital sex relationship. At the age of 15 he started to masturbate, with severe pangs of conscience. Though doing this was out of keeping with his ideals he found it very hard to check the habit.

His acne commenced when he was 15 years old.

Rosacea

A woman, aged 33, browbeaten as a child by her drunken father quiet, conscientious, scrupulous, extremely shy blushing easily and devoid of aggressiveness, had a nervous breakdown when she was 21 years old. While still in bed with this, she had a violent argument with her parents afterwards she married in haste, just to get away from home. Except for sexual matters, her married life was fairly happy for some years and she gave birth to a child. Then her husband fell in love with another woman and left her. The patient stayed on with her mother-in-law. At the age of thirty-one she met another man and, though haunted by a guilty conscience because of her daughter and her mother-in-law s disapproval, started to live with him.

I always worried inwardly. What have I done? I did not approve of anything like that. I worried such a lot I always had a gnawing feeling inwardly. How wrong it was of me. I hated myself for doing it. It blotted my copybook. I' e always led such a clean life and now I've spoilt it. Three months after living with him I got these blemishes on my face. He put it down to the fact that I didn't allow myself to enjoy myself.

Pompholyx

A sergeant, aged 38, had no doubt about his outstanding abilities. I am gifted with a ready flow of language, he said. I presume people like to hear me talk. He was one of those people who take the lead wherever they go, who suggest something even if there is nothing to suggest, and who are only really happy if they dominate the stage. He prided himself on his ability to handle people. He had been captain of a number of clubs, had taken an active part in dramatics and had written a few fairy stories. He was firmly convinced that in the not too distant future he would be so successful as a playwright that London would be at

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his feet. He admitted that his enthusiasm sometimes carried him too far and described himself as highly strung, sensitive to beauty and imaginative. Before he married he had a large number of flirtations. After one of them, two years previously which had a rather unhappy ending, he developed periodic headaches which proved intractable. According to himself he abounded in energy but he expended it to such an extent that he became easily fatigued.

Because he was a teacher his enlistment was deferred for four years. When eventually he was de-reserved he joined the Army with mixed feelings. He soon found the infantry training very fatiguing and fell out repeatedly He also reported sick with headaches many times. Within the first week of infantry training he developed pompholyx of the feet which became much worse as the training advanced so that he had to be transferred to another corps.

Psoriasis

A private, aged 29 was the daughter of a time-serving soldier She had always greatly admired her father when speaking of her mother she dismissed her as a talkative scatter brained child married to a grown-up silent man The patient was masculine in appearance. Her voice was low pitched, and her manner of speaking was more that of an old soldier than that of a woman. She used make-up and, as the conversation drew on she displayed some feminine charm.

She was a very clear and logical thinker and had a remarkable insight into her emotional difficulties She realized that she struggled a good deal inwardly There were two totally different personalities in herself one masculine and the other feminine. She watched these two personalities like an unconcerned observer and tried to laugh at them. The masculine side of her was a soldier—like her father hard and harsh the feminine side longed for affection—alas, in vain—and delighted in feminine pursuits. She loved to talk for hours to soldiers about the Army and found great pleasure in domestic arts. She had always been a woman-hater and was sexually frigid

At the age of 18 she chose to become a nurse in a children s hospital. The work was strenuous but, more important than this, to work in a female community proved irritating to her Soon afterwards she developed a patch of psoriasis which regularly disappeared when she went on holiday and came back each time she returned to duty Eventually after two years, she gave up this job and was free from psoriasis until in 1941 she volunteered for the Army Enlistment presented an emotional strain to her on three counts life in a female community did not agree with her she wanted to be a soldier and not an A.T.S girl and her aspiration to become an officer was not fulfilled.

CONCLUSIONS

Aetiology

(*a*) Irrespective of how many other and of which other factors play a part in the aetiology of skin diseases, it appears that the aetiological relevance of emotional factors has been underrated Not to explore them and not to deal with them in some instances, may be just as neglectful as not to test for albumen in the urine of a patient with a generalized oedema. Yet to omit the test would

be regarded as gross negligence, whereas omission of the former investigation is generally condoned.

(*b*) The aetiology of skin disease is probably complex, for hereditary acquired and fortuitous extraneous factors all play their part. But the detection and presence of other aetiological factors does not invalidate psychological findings, because all that psychiatrists *claim* is that there is a psychological aspect of disease which may be of little importance or all important. Evidence has been obtained which suggests that certain well-defined personality types are predisposed to develop certain skin disorders, that the time of onset of a complaint, its relapses and, to a certain extent, *its nature*, are determined by conflicts specific to the persons concerned. Some conflicts, more *than* others, have a definite bearing on the skin.

(*c*) The relevance of emotional factors in the aetiology of skin diseases varies a great deal, not necessarily from syndrome to syndrome, but often from case to case, for example, in psoriasis. *Therefore* it may not be wise to split off a group of skin disorders under the label of neurodermatoses This label arose from the belief which turned out to be erroneous, that it may be possible to make out from the appearance of a skin manifestation whether emotional factors are aetiologically relevant or not. At any rate, it would be more correct to talk about psychodermatoses than about neurodermatoses.

(*d*) There seems to be no short cut to the assessment of the aetiological relevance of emotional factors, but to carry out a careful psychiatric examination. Perfunctory questions, such as Any worries? do not lead very far Over many years psychiatrists have developed techniques of case-taking which have to be adhered to if one wants to obtain access to a patient's emotional life. Just as the knowledge of pathology is essential for the understanding of pathological lesions, knowledge of the accepted basic principles of psychopathology is essential for the understanding of psychological deviations.

(*e*) Psycho-dermatology is still very much in its infancy—to make it grow up and grow into an integral part of routine dermatology it seems necessary to extend aetiological research into disorders which have hitherto not been studied, and to make dermatologists familiar with the principles of psychiatric approach. In the foregoing an attempt has been made to introduce modern psychiatric concepts into dermatology

Relapses

To resuscitate a person who has been nearly drowned, and to treat his pneumonia if he develops that malady is sound practice, but it does not prevent him from jumping into a river again a few weeks afterwards. Yet many doctors —and this is true not only of dermatologists—go all out to treat effects rather than causes, especially as far as psychological causes are concerned. Consequently the occurrence of relapses is inevitable.

Treatment

(1) Though for some time to come, and for various reasons, systematic psychiatric examination of dermatological patients in appreciable numbers is

impossible, even a brief exploration of his patients personalities may tell a dermatologist a good deal more about the prognosis of a skin affection than the appearance of the eruption

(2) The exploration may also enable him to assess and to deal with his patient's subjective reaction to his malady and its repercussions in his social environment. A word of understanding and of wisdom may often be more effective than the most elegant ointment.

(3) Systematic psychotherapy of skin disorders, of necessity must be confined to a small selected minority A good deal of further research regarding the response of skin disorders to psychotherapy is needed. Because they lend themselves to visual control skin disorders seem to be better suited for testing the value of psychotherapy in the treatment of structural lesions than many other disorders.

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CHAPTER 12

OCCUPATIONAL DERMATOSES

LOUIS SCHWARTZ

OCCUPATIONAL dermatoses comprise about two-thirds of the occupational diseases for which compensation is paid in the United States of America.[1] This is because the skin is the largest organ of the body and the first to come in contact with external irritants.

Occupational dermatoses which are not sufficiently severe to come under the compensation laws occur even more frequently. Surveys show that about 1 per cent of all factory workers can be found with occupational dermatoses any time an inspection is made.

The more we learn of industrial processes the more we find that chemicals are important causes of dermatitis, not only among workers, but among the public who use materials processed with chemicals. It has been estimated by Oppenheim that 20 per cent of all skin diseases are of occupational origin.

PREDISPOSING CAUSES

The *stratum corneum* and the secretions of the skin constitute its defence against external irritants. The cornified cells will withstand the action of water, alcohol, certain solvents and fairly strong acids, but are attacked by alkalis and sulphides. The secretions containing cholesterol and liquid waxes form a protective coating against water-soluble irritants.

The openings of ducts and hair follicles are the vulnerable points of the skin and thinning or breaks in the epithelium are also areas of lowered resistance. All matters which impair the defence mechanism of the skin increase its susceptibility to external irritants.

Race

The Negro is less susceptible to dermatitis from dyes, coal-tar solvents, and actinic rays than is the Caucasian. The dry skin of the Mongolian makes him more susceptible to dermatitis from solvents, alkalis, and other defatting agents. The Negro, on the other hand, is more likely to develop keloids and the Mongolian is less likely to develop occupational acnes.

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[1] I am indebted to Dr. Sibyl Horner for the following information.

In Britain, at the time of writing (December 1946), the last figures to be published for Workmen's Compensation are for 1938, when cases of dermatitis produced by dust or liquids numbered 5 189 out of a total of 14 764 (i.e. 35 per cent). See Home Office, Statistics of Compensation and Proceedings under Workmen's Compensation Acts and Employers' Liability Acts, 1880. Cmd. 6201.—Editor

Among Caucasians, the blondes are said to be more susceptible to the action of solvents and brunettes with thick oily skins can better withstand the defatting action of solvents, but are more likely to develop occupational acnes from coal-tar petroleum and the solid chlorinated hydrocarbons. Various portions of the body differ in susceptibility to external irritants. The skin over the eyelids, and the inner surface of the forearm is less susceptible than the skin on the back, and the palms are comparatively rarely affected by external irritants, although they are most exposed to them

Perspiration

Those persons who perspire excessively are more prone to develop occupational dermatitis from solid substances, which only become irritants when in solution. Excessive perspiration together with friction macerates the epithelium and makes it more permeable to external irritants The *p*H of the perspiration, in so far as it affects the ability to dissolve external irritants, also plays a role in susceptibility to occupational dermatitis.

Diet

As the diet influences the *p*H of the skin and also the vitamin intake, so does it influence the susceptibility of the skin to external irritants.

Age

Young and new workers are most frequently affected with acute occupational dermatitis, but the chronic eczematoid types of occupational dermatitis usually occur among middle-aged and elderly workers.

Sex

At a hazardous job severe cases of occupational dermatitis are less frequent among women than among men partly because women are apt to notice slight irritations of the skin and seek medical aid sooner than do men and partly because women wash off dirt more frequently than do men.

Season

Occupational dermatitis is more prevalent in warm weather when but little clothing is worn and perspiration is in excess.

Uncleanliness

Wearing work clothes saturated with irritants, and lack of personal and environmental cleanliness are important predisposing causes of occupational dermatitis

Harsh cleansing agents used to remove dirt from the skin are often predisposing and actual causes of dermatitis.

ALLERGY AS A CAUSE OF INDUSTRIAL DERMATITIS

Allergy is a term coined to denote an altered reactivity of the tissues caused by contact with a substance and manifested after an interval (*period of incubation*) upon second or continued contact with the original or identical substance.

This definition implies that changes caused by first contact so condition the skin that, even though no change is observable, subsequent contact with the substance, after a period of incubation causes dermatitis. If this definition is accepted, allergy causes less than 20 per cent of occupational dermatitides.

Allergy to substances not encountered in the occupational environment has not been proved to be a predisposing cause for acquiring allergic occupational dermatitis. Allergy to one substance has not been proved to be a cause of allergy to a chemically unrelated substance.

Most cases of industrial dermatitis develop on new workers within a few days or weeks after they begin work in an occupation in which there is a skin hazard. If the skin hazard consists of a primary skin irritant, the worker soon learns to protect himself by proper protective clothing, frequent removal of the irritant by washing, the use of protective ointments and taking care to avoid unnecessary contact with the irritant. If he does not take these precautions he will continually be affected with industrial dermatitis.

If the skin hazard consists of a sensitizer and the dermatitis is not sufficiently severe to prevent the patient from working, he will in most instances develop a tolerance or hyposensitivity in from three to six weeks. The workers call this hardening

Some workers with dermatitis so severe that they cannot work may also develop a tolerance after they recover and can return to work without further trouble. Others may develop less severe dermatitis upon return to work and may later develop a tolerance. There are a few workers, less than 10 per cent of those affected with allergic occupational dermatitis, who cannot develop a tolerance and must change to other occupations.

There are a few workers, mostly older men, who after having worked for many years without dermatitis at an occupation having a skin hazard, suddenly break out in a more or less generalized allergic industrial dermatitis. Such workers seem to have lost their hyposensitivity and they never regain it. They can get well only if they give up or change their employment.

The writer's experience does not bear out the theory advanced by some dermatologists that, as a result of occupational allergy a worker may develop allergy to entirely unrelated substances. Neither does the writer subscribe to the theory that allergic monosensitivity predisposes to allergic polysensitivity Experience shows the contrary for workers who develop an allergy to a chemical tend to lose their sensitivity and become relatively immune to it. Allergies are highly specific they are as specific as immunities. A worker sensitized to a chemical is allergic only to that chemical or to one that is chemically closely related. A parallel to these facts exists in clinical medicine thus a person immunized to typhoid is not immune to cholera, but a person immune to vaccinia has an immunity to variola. I have known workers so allergic to one chemical that their skin tingled when they entered a room containing a bottle of that chemical, but they were not allergic to any other chemical.

It is true that, as we grow old, atrophic changes occur in the structures responsible for the defence of the skin—the epithelial layer and the glands—and

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Those persons who perspire excessively are more prone to develop occupational dermatitis from solid substances, which only become irritants when in solution. Excessive perspiration together with friction, macerates the epithelium and makes it more permeable to external irritants. The *p*H of the perspiration, in so far as it affects the ability to dissolve external irritants, also plays a role in susceptibility to occupational dermatitis.

Diet

As the diet influences the *p*H of the skin and also the vitamin intake, so does it influence the susceptibility of the skin to external irritants.

Age

Young and new workers are most frequently affected with acute occupational dermatitis, but the chronic eczematoid types of occupational dermatitis usually occur among middle-aged and elderly workers.

Sex

At a hazardous job severe cases of occupational dermatitis are less frequent among women than among men partly because women are apt to notice slight irritations of the skin and seek medical aid sooner than do men and partly because women wash off dirt more frequently than do men.

Season

Occupational dermatitis is more prevalent in warm weather when but little clothing is worn and perspiration is in excess.

Uncleanliness

Wearing work clothes saturated with irritants, and lack of personal and environmental cleanliness are important predisposing causes of occupational dermatitis.

Harsh cleansing agents used to remove dirt from the skin are often predisposing and actual causes of dermatitis.

ALLERGY AS A CAUSE OF INDUSTRIAL DERMATITIS

Allergy is a term coined to denote an altered reactivity of the tissues caused by contact with a substance and manifested after an interval (period of incubation) upon second or continued contact with the original or identical substance.

This definition implies that changes caused by first contact so condition the skin that, even though no change is observable, subsequent contact with the substance, after a period of incubation, causes dermatitis. If this definition is accepted, allergy causes less than 20 per cent of occupational dermatitides.

Allergy to substances not encountered in the occupational environment has not been proved to be a predisposing cause for acquiring allergic occupational dermatitis. Allergy to one substance has not been proved to be a cause of allergy to a chemically unrelated substance.

Most cases of industrial dermatitis develop on new workers within a few days or weeks after they begin work in an occupation in which there is a skin hazard. If the skin hazard consists of a primary skin irritant, the worker soon learns to protect himself by proper protective clothing, frequent removal of the irritant by washing, the use of protective ointments and taking care to avoid unnecessary contact with the irritant. If he does not take these precautions he will continually be affected with industrial dermatitis.

If the skin hazard consists of a sensitizer and the dermatitis is not sufficiently severe to prevent the patient from working, he will in most instances develop a tolerance or hyposensitivity in from three to six weeks. The workers call this hardening

Some workers with dermatitis so severe that they cannot work may also develop a tolerance after they recover and can return to work without further trouble. Others may develop less severe dermatitis upon return to work and may later develop a tolerance. There are a few workers, less than 10 per cent of those affected with allergic occupational dermatitis, who cannot develop a tolerance and must change to other occupations.

There are a few workers, mostly older men, who after having worked for many years without dermatitis at an occupation having a skin hazard, suddenly break out in a more or less generalized allergic industrial dermatitis. Such workers seem to ha e lost their hyposensitivity and they never regain it. They can get well only if they give up or change their employment.

The writer's experience does not bear out the theory advanced by some dermatologists that, as a result of occupational allergy a worker may develop allergy to entirely unrelated substances. Neither does the writer subscribe to the theory that allergic monosensitivity predisposes to allergic polysensitivity Experience shows the contrary for workers who develop an allergy to a chemical tend to lose their sensitivity and become relatively immune to it. Allergies are highly specific they are as specific as immunities. A worker sensitized to a chemical is allergic only to that chemical or to one that is chemically closely related. A parallel to these facts exists in clinical medicine thus a person immunized to typhoid is not immune to cholera, but a person immune to vaccinia has an immunity to variola. I have known workers so allergic to one chemical that their skin tingled when they entered a room containing a bottle of that chemical, but they were not allergic to any other chemical.

It is true that, as we grow old, atrophic changes occur in the structures responsible for the defence of the skin—the epithelial layer and the glands—and

thus the skin becomes more vulnerable to external irritants, be they primary irritants or sensitizers as a result the skin may be affected by stimuli which previously did no harm Some elderly workers, once they develop dermatitis may always thereafter be affected by minor stimuli but this condition is the natural result of age and not of occupation Any occupational exposure which injures or breaks down the defence mechanism of the skin will also make it more sensitive to external irritants, and as a result, the worker may be affected by chemicals which formerly he could tolerate easily Such a polysensitivity is not necessarily due to allergy If the worker is young enough after he is removed from the irritant environment the injured skin can repair its defences and may again tolerate the hazard.

During the period when the skin is recovering it may react to minor stimuli and the period of recovery may be prolonged.

Patch tests on such persons are unsatisfactory sometimes they are impracticable, especially on older workers, because the patient may be feeble and the risk of a flare-up of the lesions cannot be taken or there may not be any normal areas of skin suitable for patch testing. Such a skin may react to anything used in the form of a patch test, and if patch tests are positive with substance occupationally encountered the conclusion that the dermatitis is of occupational origin may be wrong it cannot be denied, however that the occupation is a contributing factor to the continuation of the dermatitis

It has been argued by those who believe that one allergy predisposes to other allergies that if the patch test is negative to substances occupationally encountered, and positive to substances encountered outside the occupational environment, the worker must first have developed the allergy to the occupationally encountered substance, and as a result, must have become allergic to non-occupationally encountered substances, but the first allergy was then lost and only the later acquired allergy to non-occupationally encountered substances remained If such a contention is supported then every allergic condition in a worker which manifests itself after he is once employed could be regarded as being due to his occupation. Such reasoning is absurd because workers can become allergic to substances encountered outside their occupational environment.

Even if it was admitted that one allergic monosensitivity predisposes to other allergies, it would still be impossible to determine whether a chronic persistent poly-allergic dermatitis in a worker was the result of a first acquired occupational allergy or of an acquired non-occupational one.

Multiple allergies causing generalized allergic eczemas can and sometimes do occur among people exposed to sensitizers outside the working environment. If such a worker also shows a positive patch test to a substance occupationally encountered, his occupation can be rightly considered as contributing to the persistence of his dermatitis.

ACTUAL CAUSES

Mode of action

These can be divided according to their mode of action into two large groups

(1) primary irritants which cause about 80 per cent of all occupational dermatoses

(2) sensitizers, which cause about 20 per cent of occupational dermatoses.

(a) Primary irritants

Primary irritants are agents which cause dermatitis by direct action at the site of contact, provided they act in sufficient intensity or quantity for a sufficient time. Primary irritants have a definite physical or chemical action on the skin.

(b) Sensitizers

Sensitizers do not necessarily cause demonstrable cutaneous changes on primary contact, but may effect such specific changes in the skin that, after an incubation period of several days or months, further contact will cause dermatitis. A substance can be both a primary irritant and a sensitizer

Causes of occupational dermatitis

The causes of occupational dermatitis can also be classified according to their nature into five main groups.

(1) Mechanical causes such as friction, pressure, trauma.[1]

(2) Physical causes heat, cold, sunlight, electricity x-rays, radium.

(3) Chemical causes inorganic and organic.

(4) Poisonous plants Anacardiaceae, etc.

(5) Biologic agents bacteria, fungi, animal parasites.

(1) *Mechanical*

Mechanical agents can cause lacerations, abrasions, and callosities, any of which may become infected.

(2) *Physical*

Exposure to high temperatures may cause erythema telangiectases and intertrigo. Exposure to cold may produce frost-bite and, in rare instances, urticaria. Solar radiation in excess, as in the tropics, at the sea-side, or in high altitudes, may cause proliferative skin changes, especially in blondes.

Radium and x-ray burns may occur among physicians and technicians. Since the introduction of x-rays into industry to detect flaws in metals and fruit, workers exposed to x-rays may develop x-ray burns.

Radio-active substances such as radium, mesothorium, uranium, and so on, may cause burns among exposed industrial workers, such as watch-dial makers, etc.

(3) *Chemical*

These agents are the principal causes of industrial dermatoses. They may be divided into two classes inorganic and organic.

Each of these can be subdivided into *primary irritants* and *sensitizers*.

Inorganic primary irritants[2] are such substances as

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[1] Lesions at sites of occupational trauma among psoriatics and those suffering with lichen planus (Koebner phenomena) have been deemed occupational.

[2] For more complete list of primary irritants the reader is referred to *Occupational Diseases of the Skin* Louis Schwartz *et al.* Lea and Febiger Philadelphia, Pennsylvania, United States of America.

(1) the strong acids sulphuric, nitric, hydrochloric hydrofluoric, chromic, etc.

(2) the strong alkalis, such as sodium and potassium hydroxide sodium car bonate, calcium oxide, etc

(3) reducing agents, such as sodium, potassium, and calcium sulphides

(4) certain corrosive salts, such as the mercuric salts zinc chloride, alka line bichromates, salts of arsenic and antimony silver nitrate, fluorides, etc.

Organic primary irritants are such chemicals as

(1) organic acids and anhydrides, well-known examples of which are *acetic, carbolic, cresylic, formic, thioglycollic*, lactic oxalic, and salicylic acids

(2) organic alkalis, such as, ethanol amines, methylamines

(3) organic solvents, such as petroleum solvents, coal-tar solvents, chlorinated hydrocarbon solvents, esters, turpentine alcohols, carbon bisulphide,

(4) essential oils of irritant plants, such as urushiol cardol, bhilawanol

(5) acne producers, such as crude petroleum, heavy petroleum oils, pitch, tar solid chlorinated hydrocarbons.

Sensiti ers These usually affect only a small percentage of exposed workers, but massive exposure for a long time will sensitize a larger percentage. A few of the sensitizers can sensitize everyone if there is sufficient exposure.

The tendency to become hypersensitive may be inherited, but the actual occupational allergy is acquired by exposure to the sensitizing substance.

Almost any chemical can be a sensitizer but some have greater sensitizing properties than others. Phenol, formaldehyde, and the alkaline bichromates are notorious sensitizers as well as primary irritants. Many other primary irritants are also strong sensitizers

Examples of industrial sensitizing chemicals are as under

(1) Dye intermediates, such as dinitrochlorbenzol, benzanthrene, nitrosodimethylaniline, phenyl glycine.

(2) Dyes, such as *p*-phenylenediamine bismarck brown chrysoidine, amidoazotoluene, metaniline yellow rosaniline.

(3) Photo developers, such as Metol paramidophenol bichromates, para formaldehyde

(4) Rubber compounds, such as hexamethylenetetramine, tetramethylthiurambisulphide, mercaptobenzothiazole, phenyl-*beta*-naphthylamine.

(5) Insecticides, such as pyrethrum, rotenone, organic mercuric salts, thiocyanates.

(6) Oils, such as mustard oil, cashew nutshell oil coconut oil essential oils of many plants.

(7) Natural resins, such as pine rosin, Japanese lacquer

(8) *Synthetic resins, such* as phenolformaldehyde urea formaldehyde, alkyd ester-gums, and resin plasticizers and stabilizers

(9) Explosives, such as trinitrotoluene, Tetryl *fulminate of mercury* picric acid and picrates.

(10) Photosensitizers, such as oil of bergamot coal-tar pitch, fluorescein fig sap, citrus oils

(4) *Plants*

There are many *families of plants* that have irritant members, but the Anacardiaceae furnish the largest number of irritant plants. Poison ivy cashew-nutshell

oil, Japanese lacquer litre, poison sumac belong to this family. In Europe the primrose also has been reported often as a cause of dermatitis. The active irritants in many of the plants are primary irritants and have the chemical nature of phenols, terpenes, and aldehydes. The woods of many trees are potent sensitizers. Examples of these are coco bolo, boxwood, mahogany, Brazilian walnut, rengas wood, cedar, redwood, satinwood, and cocus wood.

(5) *Biologic agents*

These may be classified as (1) bacterial infections, (2) fungus infections, and (3) parasitic infections.

The principal bacterial types of occupational dermatoses are

(1) bacterial infection of occupational wounds
(2) erysipeloid in meat and fish handlers
(3) anthrax in leather workers
(4) verruca necrogenica in cadaver and meat handlers
(5) vaccinia in cattle handlers
(6) butcher's pemphigus
(7) glanders.

Fungi which may cause occupational dermatoses are

(1) monilia in kitchen workers
(2) yeast in bakers and fruit handlers
(3) dermatophytes in animal handlers and beauticians
(4) deep fungus infections in horticulturists.

Parasites chiefly causing occupational dermatoses are

(1) *Tyroglyphus longior* (cheese mite)
(2) *Ascaris lumbricoides* (hog itch)
(3) *Carpoglyphus passularum* (grocers)
(4) *Pediculoides ventricosus* (grain itch)
(5) mange (dog handlers)
(6) *Uncinaria* (ground itch).

PATHOGENY

Prosser White (1934) suggested that the action on the skin of the chemical causes of dermatoses could be classified as follows

(1) keratin solvents, as the alkalis
(2) fat solvents, as the petroleum solvents
(3) hydroscopic agents, as the strong acids
(4) protein precipitants, as the heavy metal salts
(5) oxidizers, as the per salts
(6) hydrolyzers, as calcium oxide
(7) reducing agents, such as the sulphides
(8) keratogenic agents, such as coal-tar and petroleum
(9) sensitizers, such as organic nitro-compounds and chloro-compounds
(10) photosensitizers, such as oil of bergamot, eosin, and coal-tar

SYMPTOMATOLOGY

Acute occupational dermatitis begins with pruritus of the exposed parts. This is usually followed by erythema oedema, papules, vesicles, crusts, and desquamation

The process may become arrested or stationary at any of these stages.

The most exposed or most tender parts of the skin are first affected. Unexposed parts are only affected in cases of allergic contact dermatitis, when there is *also absorption of the* substance into the system and deposition of it in the skin.

Mild cases are most frequent and the worker usually continues at his work.

In most cases of allergic dermatitis a hyposensitization or hardening develops in the course of three or four weeks and the worker can continue to work without further trouble this, of course, does not take place when the causative chemical acts as a primary irritant. The hyposensitization which develops in cases of allergic dermatitis is directly proportionate to the amount of exposure if the exposure is suddenly increased after hyposensitivity has developed, dermatitis may again develop and may again be followed by hyposensitization to the *increased* exposure.

All *cases of allergic dermatitis do not develop hyposensitization*. Some workers, who for many years have been hyposensitive may suddenly develop an allergic dermatitis from the chemicals to which they were hyposensitive. Such workers as a rule remain allergic to these chemicals ever after

Long-continued exposure to mild primary irritants such as soaps, solvents, and dehydrating agents causes mild irritation followed by a gradual thickening, *drying*, and cracking of the skin.

Ulcers are caused by the action of strong primary irritants especially on the broken skin. Sodium carbonate lime, chromic acid, zinc chloride, and fluorides are notorious for the frequency with which they produce ulcers

Acne like lesions and comedones occur as a result of exposure to coal-tar and pitch, crude petroleum, and the heavier oils, and to the solid chlorinated hydrocarbons

Keratoses and epitheliomas are caused by excessive exposure to sunlight, x rays, radium coal tar pitch and soot. *Alpha*-naphthylamine, an intermediate in dye manufacture, causes papilloma of the bladder

Photosensitization exposure to or ingestion of some plants and chemicals causes the skin to become hypersensitive to sunlight. The oil of bergamot was first reported to have this action. We know now that many citrus oils, some grasses, and the sap of figs can also cause photosensitization Eosin and some of its derivatives, the fluorescent dyes, coal tar and pitch are other photosensitizing agents.

DIAGNOSIS

The diagnosis of occupational dermatitis should be based on the following data (1) history (2) site of eruption (3) pattern of the lesions (4) patch tests.

History

The history of the dermatitis should show that it developed during or shortly after the period of occupational exposure. It should also show that some other workers similarly exposed have been similarly affected and that the dermatitis improves when the patient is not at work and becomes worse when he returns to work.

Occupational dermatitis should improve when the worker is away from work, unless the irritant is also encountered in the non-occupational environment. In the latter case it is impossible to determine whether the initial cause was occupational or not. When a case of supposedly occupational dermatitis does not recover or at least show marked improvement after a reasonably long absence (about 2 months) from work, the cause of the dermatitis should also be sought elsewhere than in his occupational environment. Recurrent attacks of dermatitis occurring during long absences from work certainly suggest a possible non-occupational aetiology.

Site of eruption

Occupational dermatitis begins on the most exposed parts, usually the hands, fingers, and forearms if the irritant is a liquid or solid, and on the face and neck if the irritant is a dust, mist, or fume. The covered parts of the body may also be affected if the irritant penetrates or saturates the clothing.

Occupational dermatitis frequently begins at sites of friction from the clothing. The wrist may be affected from being rubbed by soiled gloves and sleeves; the waist, from friction with the belt; the ankle, from friction with shoe tops; the neck, from friction with the collar.

Generalized occupational eruptions sometimes occur as a result of contact of large portions of the body with allergenic substances, as, for instance, when the worker becomes enveloped in the dust or fumes of well-known sensitizers such as organic nitro-compounds. Generalized eruptions may also develop from the ingestion or inhalation of toxic chemicals; these occurred among workers and soldiers from quinacrine hydrochloride U.S.P. XII (Atabrine; mepacrine hydrochloride B.P.).

Pattern of the lesions

While the acute eczematoid types of occupational dermatitis are not characteristic of any one class of irritants, certain occupational irritants produce characteristic lesions; for example, the paronychia of fruit and vegetable canners; the acne-like lesions caused by the chloronaphthalenes, chlorodiphenyls, heavy coal-tar distillates, and heavy petroleum distillates; the keratotic lesions caused by actinic rays, crude petroleum, and coal-tar; the papillomas of the bladder which occur in dye-makers and which are caused by long exposure to *alpha*-naphthylamine.

The patch test

This test is valuable in finding the actual substance that is causing an allergic contact dermatitis. If only a few workers, among many engaged on a particular

job are affected with dermatitis, then patch tests should be performed on them with the sensitizing substance which they encounter to determine the actual irritant. A few of the non-affected workers should be patch tested for control purposes.

Reactions to the patch test depend upon

(1) the degree of sensitivity

(2) the concentration of the substance used,

(3) the time it remains in contact with the skin

(4) the amount of substance used on the patch test site.

In performing patch tests, constant definite concentrations and amounts of the suspected substance should be used on constant definite areas of skin, for a constant definite time. With this technique the intensity of the reaction varies only with the degree of sensitivity of the patient.

The diagnostic patch tests should be performed as follows

With liquids saturate a piece of gauze 1 inch square, 4 plys thick, with the liquid squeeze out the excess liquid so that it does not drip and apply the gauze to the normal skin of the arm, leg, back, or front of chest cover the gauze with a piece of non-waterproof Cellophane 2 inches square. Seal this to the skin with a piece of adhesive plaster 3 inches square.

With powders place the powder on a similar piece of gauze, first moistened with water, and proceed as above.

With solids these can be powdered or if they are soluble, they can be dissolved in definite concentrations, and a piece, 1 inch square, of 4-ply gauze can be saturated with the solution and allowed to dry so that none of the solvent remains on the gauze. Then proceed as above. When the solid is of a resinous character the solution containing it may be painted on the skin, the solvent allowed to evaporate, and the dry film of resin can be covered with Cellophane and adhesive plaster as above.

When the degree of sensitivity to primary irritants such as solvents is to be ascertained the solvent should be diluted with various definite amounts of a bland oil such as corn oil or liquid paraffin in order to buffer its primary irritant action, and applied as described for the liquid patch tests.

It is usual to permit the patches to remain on the skin for 24 hours, but this may be varied according to the concentration of the irritant and the subjective symptoms of the patient For more details of concentrations to be used for patch testing see Rostenberg and Sulzberger (1939)

The reactions should be read upon removal of the patches and daily thereafter for three days so that delayed reactions and the behaviour of early reactions may be noted A true allergic reaction persists for several days, sometimes for weeks.

According to Schwartz and Peck (1935) the mechanical irritation from adhesive plaster soon fades.

There are many modifications of the patch test, but the above is the simplest and most adaptable for general use.

In recording the results of a patch test a simple erythema at the site of the patch is graded as 1+ erythema and oedema as 2+ erythema oedema, and papules with a few vesicles as 3+ erythema, oedema, many vesicles, and perhaps an ulcer as 4+

A delayed reaction appearing 24 hours to 72 hours after the removal of the patches denotes sensitivity to a lesser degree than an immediate reaction, provided the concentration of the irritant, the size of the patch, and the amount of the irritant are the same. A true allergic reaction increases in intensity for 24–48 hours after it appears and persists for several days. Many patients develop reactions to the adhesive plaster These must not be confused with reactions from the allergen, from which they are separated by a clear zone of skin which only came in contact with the insulating Cellophane.

A negative reaction does not entirely rule out the fact that the patient was sensitive to the test substance at the time he developed dermatitis, because (1) the conditions of the patch test may not be so severe as was the actual occupational exposure (2) the patient may no longer be sensitive, and (3) the actual substance causing the dermatitis may not have been applied in the patch test.

Reactions are most likely to result from patch tests at the time when the dermatitis is still present and active, and on areas where the keratin layer is thin.

Although flare-up of quiescent areas of dermatitis may result from patch tests, generalized eruptions rarely occur and systemic symptoms are even more rare.

Patch tests for diagnostic purposes should not be performed with primary irritants except in such dilutions as are known to have no effect on the normal skin. Patch tests should not be performed with allergens with which the patient has not had previous contact, because of the possibility of inducing allergy

Pre-employment patch tests are not advisable, because they only weed out those who are sensitive already to the substances they will encounter in the course of their new employment. Such sensitive persons will be few because sensitivities are acquired by previous contact. Pre-employment patch testing will not foretell who may become sensitized, nor does it take into consideration the fact that most of the new workers who develop an allergic occupational dermatitis will become hyposensitive after a few weeks.

TREATMENT

Most cases of industrial dermatitis are mild, and occur in new workers. A non-irritating protective ointment applied to the affected parts and the use of protective clothing over the anointed skin will usually be sufficient to keep the worker on the job until the dermatitis disappears, a matter of two or three weeks. If the dermatitis does not improve under this treatment the worker should be removed from the job. This should and usually does result in recovery If recovery does not occur after a reasonably long period of absence from work (two months) the cause of the dermatitis must also be sought elsewhere than in his occupation.

Severe cases of dermatitis should be removed from work and treated with wet dressings until the acute symptoms subside. Such dressings can be used in the form of compresses of a saturated solution of boric acid or Burow's solution 1 20. After the acute symptoms subside, a soothing ointment should be applied. Such ointments are zinc oxide ointment, boric acid ointment, a mixture of equal parts of cold cream and lanolin, etc.

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(1) free solubility in hard, soft, cold, and hot water
(2) ability to remove all types of dirt without damaging the skin
(3) it should not, with normal usage, remove from the skin an undue amount of its natural fats
(4) it should not contain abrasive scrubbers
(5) it should be handy to use if in cake form, or flow easily through soap dispensers if in granulated, powdered, or liquid form
(6) it should not deteriorate or be liable to infestation with insects
(7) it should not clog the plumbing.

A superfatted toilet soap, containing a synthetic detergent and a soft vegetable scrubber will answer the above requirements

Type formula for industrial cleanser

Toilet soap	50 parts
Colloidal clay (kaolin or bentonite)	20 ,,
Duponol	20 ,,
Lanolin	5 ,,
Perfume	1 ,,

This may be used in cake form, or 25 parts of corn meal may be added and the mixture ground to make a powdered soap.

A liquid cleanser can be made by mixing equal parts of a potassium-coconut oil soap and sulphonated castor oil, and adding 1 per cent of Aerosol O T to the mixture.

Workers who are sensitive to soap, or who have eczematous skins, should not use soap Such workers should use oily mixtures such as the formula given below

Neutral sulphonated castor oil	93 parts
Pure castor oil	5 ,,
Synthetic detergent	2 ,,

Strongly alkaline reinforced soaps, or soaps containing powerful solvents or abrasives, need not be used to remove adherent and water-insoluble soil from the skin. According to Schwartz and Mason (1945), a mixture of Aerosol O T parts 10 and light white petroleum oil having a B.P 150°–200° C., will quickly remove heavy petroleum and tar fractions the mixture itself can be quickly and easily removed by flushing with water The stains of synthetic dyes can be removed by soaking the hands for 2–3 minutes in 1 2,000 potassium permanganate solution, and then removing the stain of the permanganate by immersing the hands in a 1 per cent solution of sodium sulphite. The hands can then be washed in water dried, and an emollient rubbed into the skin. Such an emollient is anhydrous lanolin and cold cream, equal parts.

Protective clothing

Properly designed protective clothing will prevent irritants from touching the skin. Impervious materials such as the synthetic plastic films and rubber will

Lotions or ointments containing irritant or stimulating drugs should be used only on long-standing cases and only then after carefully considering the possibility of irritating an already inflamed skin. There is no reason to use such drugs as mercury sulphur coal-tar etc. on an uncomplicated acute case of dermatitis venenata Neither is there any reason for the use of the sulphonamide drugs and antibiotics unless the dermatitis is complicated by bacterial infection. Trifling eruptions have been converted into serious ones by such mistreatment.

When there is dry scaly eczematization or lichenification as may occur in a dermatitis of long standing, then the use of stimulating therapy such as salicylic acid 3–5 per cent in an ointment base, fractional doses of unfiltered x-rays, and so on is indicated according to the judgement of the dermatologist.

Analgesic agents, such as menthol phenol, and benzocaine, should be used with caution to allay itching, for they are well known sensitizers. Relief from pruritus may be obtained by warm baths containing corn starch bran, or oatmeal. The efficacy of the anti-histamine drugs such as Benadryl and Pyribenzamine in stopping the pruritus of an occupational allergic dermatitis has yet to be proved, but in severe cases when other measures fail, they are worth trying.

Desensitization against allergic industrial irritants by means of subcutaneous injections of ascending doses of the allergen has not met with success except perhaps against poison ivy

THE PREVENTION OF OCCUPATIONAL DERMATOSES

New applicants who have skin diseases should not be placed in occupations in which there are marked skin hazards Pre-employment patch testing is not advised for the reasons given previously The best preventive measures are those which best prevent contact of potential irritants with the skin. Safety engineering-control measures, such as totally enclosed processes, general ventilation of work rooms and special suction vents to carry away irritant dusts, vapours, and gases, should be used wherever possible. Suction vents so badly placed that the irritant vapours are drawn past the worker have often added to instead of taken away an industrial hazard. Respirators gas masks, and air intake hoods should be supplied by the management to workers exposed to irritant dusts, gases, and vapours. They should be cleansed daily and kept in good repair by the management. The presence of noxae in the working environment should be periodically checked by sanitary engineers.

The most effective personal protective measure is cleanliness This includes not only personal hygiene, but environmental cleanliness as well. Floors, walls, ceilings, windows, machinery and tools should be kept clean and free of irritants. Enough shower baths with hot and cold water soap and towels should be provided so that all the workers going off a shift can take a shower and change to street clothes in a reasonable time (e.g. half an hour) Many large industrial establishments now pay the workers for the half hour spent in personal cleansing.

Dermatitis sometimes results from the use of harsh cleansers used to remove industrial dirt. The use of harsh soaps containing added alkali solvents, or abrasives should be discouraged An industrial cleanser should at least have the following properties

(1) free solubility in hard, soft, cold, and hot water
(2) ability to remove all types of dirt without damaging the skin
(3) it should not, with normal usage, remove from the skin an undue amount of its natural fats
(4) it should not contain abrasive scrubbers
(5) it should be handy to use if in cake form, or flow easily through soap dispensers if in granulated, powdered, or liquid form
(6) it should not deteriorate or be liable to infestation with insects
(7) it should not clog the plumbing.

A superfatted toilet soap, containing a synthetic detergent and a soft vegetable scrubber will answer the above requirements.

Type formula for industrial cleanser

Toilet soap	30 parts
Colloidal clay (kaolin or bentonite)	20 "
Duponol	20 "
Lanolin	5 "
Perfume	1 "

This may be used in cake form, or 25 parts of corn meal may be added and the mixture ground to make a powdered soap.

A liquid cleanser can be made by mixing equal parts of a potassium-coconut oil soap and sulphonated castor oil, and adding 1 per cent of Aerosol O T to the mixture.

Workers who are sensitive to soap, or who have eczematous skins, should not use soap Such workers should use oily mixtures such as the formula given below

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Protective clothing

Properly designed protective clothing will prevent irritants from touching the skin. Impervious materials such as the synthetic plastic films and rubber will

protect against liquids vapours, and dusts Rubber gloves, aprons, boots, and sleeves are proof against penetration by water-soluble irritants. Synthetic rubbers are more resistant to oils and solvents than natural rubber Pliofilm, Koroseal, and Vinylite will prevent penetration of water soluble and oil-soluble irritants, but are attacked by the chlorinated hydrocarbon solvents such as carbon tetrachloride and trichlorethylene. Resistoflex films (polyvinyl alcohol) will resist penetration by the chlorinated hydrocarbons. In making protective clothing from the synthetic films, the possibility of dermatitis from the films can be prevented by lining that part of the garment which closely touches the skin with a soft fabric, such as flannel or cotton Closely woven overalls will keep out coarse irritant dusts Protective clothing to be effective as a preventive against dermatitis must be kept in good repair and cleaned daily Therefore it should be furnished, repaired and laundered by the management of the factory

Protective ointments

Protective ointments are not as efficient preventives as are protective clothing and cleanliness but sometimes they may be the only protection available. When protective ointments are used, the workers rarely leave the factory without washing them off therefore these ointments are of some value if only because they ensure that the workers wash after work.

Protective applications can be classified into two large groups (1) those which are water repellent, and (2) those which are oil repellent. Each of these groups may be subdivided into the ointment film type and the dry film type.

The water repellent films give protection against acids, alkalis, and water soluble irritants The oil repellent films give protection against oils, solvents, and oil-soluble irritants. The water repellent oily ointments contain an animal fat like lanolin or a mineral fat like petrolatum (soft paraffin), sometimes a vegetable oil like castor oil, and perhaps some stiffening agent such as beeswax, carnauba wax, spermaceti paraffin wax, etc Below is the type formula of such an ointment

Type formula of a water-repellent ointment

Anhydrous lanolin – – – – – – – –	60 parts
Castor oil – – – – – – – –	30
Spermaceti – – – – – – – –	10
Preservative – – – – – – – –	q.s.

A water repellent dry film application consists essentially of a water insoluble resin dissolved in alcohol In order to give it body and to reinforce the resin film which remains on the skin after the alcohol evaporates, inert powders may be added Below is the type formula of such an application.

Type formula of a dry film water-repellent application

Shellac – – – – – – – – –	10 parts
*Iso*propyl alcohol – – – – – – –	65
Talc – – – – – – – – –	13 ,,
Sodium perborate – – – – – – –	10
Boric acid – – – – – – – –	2

The oil-repellent and solvent-repellent applications of the ointment type consist of water-soluble resins (such as tragacanth, acacia, sodium silicate, Irish moss, sodium alginate, pectin, methyl cellulose) in a vanishing-cream type of base, or simply dissolved in water

Type of oil-repellent or solvent-repellent ointment

Sodium alginate	5 parts	
Tragacanth	5 "	
Stearic acid	20 "	Vanishing cream
Sodium carbonate	2 "	
Glycerin	5 "	
Water	63 "	

Type of oil-repellent or solvent-repellent dry film

Acacia	10 parts
Borax	2 "
Water	88 "

Mild alkalis such as magnesium oxide may be incorporated in protective applications to help to neutralize acids mild acids such as boric acid may be added to help to neutralize alkalis.

Per salts such as the perborates, peroxides, permanganates, and so on may be incorporated into the protective applications in order to help to oxidize and destroy the irritant properties of certain substances.

Chemical light filters, such as menthyl salicylate, the anthranilates, isobutyl paraminobenzoate, cinnamates, tannates, etc., may also be incorporated to protect against ultra-violet rays and photosensitization.

Protective ointments in general should have the following properties.

(1) They should be non-irritating and non-sensitizing.

(2) They should give actual protection against the irritant.

(3) They should be easily applicable to the skin.

(4) They should adhere to the skin during work and yet be easily removed with non-irritant cleansers after work.

(5) They should not deteriorate in the containers.

The skin should be cleansed before each application of a protective ointment in order to prevent sealing of irritants on the skin.

OCCUPATIONAL MELANODERMA

The principal causes of occupational melanosis are excessive exposure to actinic rays, coal-tar and its heavier distillates, crude petroleum and asphalt. These substances are photosensitizers, and nearly all workers, even Negroes, exposed to the dust or vapours of coal-tar complain of burning of the skin when exposed to bright sunlight. Many of the workers with coal-tar also have a deep yellowish-brown

colour of the exposed portions of the skin. This pigmentation is due partly to the discoloration of the epidermis by the coal-tar and *partly to an excessive amount of* melanin in the basal layer of the epithelium as shown by the dopa reaction (Foerster and Schwartz, 1939)

A few workers, especially blondes, exposed to the fumes of coal-tar pitch develop an urticarial type of eruption. The blonde types sometimes fail to develop melanosis, and the photosensitivity may become so severe that they must leave their work Apparently the melanosis is a protective mechanism against the photosensitization

The principal occupations in which melanosis occurs from coal tar and crude petroleum are as follows

(1) Those working with heavy coal-tar distillates and pitch in coal-tar distillation plants

(2) Workers impregnating paper tubing or pipes with coal-tar pitch.

(3) Workers painting with heavy coal tar distillates, as in rust-proofing iron piping.

(4) Road making, especially those requiring boiling pitch and asphalt.

(5) Briquette manufacture, in which coal tar pitch is used to make briquettes from coal dust.

(6) Petroleum refineries, especially among workers removing the residual asphalt from the stills and those cleaning the residue from the cracking coils.

Workers exposed to excessive amounts of actinic rays also develop melanosis. The hyper pigmentation is due partly to the formation of extra melanin in the basal layers and partly to thickening of the *stratum corneum.*

Farmers sailors, and other workers exposed to large amounts of sunlight are often affected by actinic ray hyper pigmentation

Technicians exposed to actinic rays from quartz lights and those exposed to x rays may also develop melanotic skin changes.

Exposure to some plants, either by contact or ingestion, also causes photosensitization Below is a list of these plants.

Agave lechuguilla	
Fagopyrum esculentum	Buckwheat
Fagopyrum tataricum	India wheat
Ficus	Figs (the noxious agent is the milky sap)
Hypericum perforatum	St. John s wort
Hypericum crispum	(Hypericin and hypericum red are fluorescent chemicals)
Medicago denticulata	Bur clover
Nolina texana	Bunch grass
Polygonum persicaria	Lady's thumb
Tetradymia canescens	Rabbit bush

Tetradymia glabrata	
Tribulus terrestris	Puncture vine
Trifolium hybridum	Alsike clover
Citrus	(Bergamot) (Berlocque dermatitis)
Citrus	(Lemon grass)
Citrus	(Limes)
Mentha citrata	Bergamot mint
Daucus carota	Wild carrot
Dictamnus albus	Gas plant

A melanosis occurring during World War I was described in 1921 by Riehl and Kerl, and was generally attributed either to the lack of vitamin B complex as in pellagra or to a photosensitivity produced by eating photosensitizing foods.

Occupational pigmentations are not as common as the melanoses. Coal-miners may have minute pieces of coal embedded in the skin.

Silver gold, mercury and other metals deposited in the skin gain access through the blood and body fluids, and not from occupational contact.

OCCUPATIONAL LEUCODERMA

Schwartz, Oliver and Warren (1940) described an outbreak of leucoderma among leather workers which was traced to monobenzyl ether of hydroquinone, an anti-oxidant, used in rubber gloves worn by the workers.

The chemical inhibited the formation of melanin in the basal layers of the epithelium, at the site of contact, as was distinctly shown by the dopa reaction. The leucoderma could be reproduced on Negro skin by applying the chemical contained in rubber for several weeks, or by painting an acetone solution of the chemical on the skin daily for several weeks. Depigmentation of the skin occurs in scars, areas of atrophy scleroderma, and morphea, but monobenzyl ether of hydroquinone is the only known chemical which, when applied to the skin causes leucoderma without otherwise injuring it.

The colour of the hair on the leucodermatous area was not affected and re-pigmentation began several months after contact with the chemical had ceased. The re-pigmentation began in the skin round the hair follicles and spread peripherally from there.

INDUSTRIAL ACNE

This is one of the most frequent forms of industrial dermatitis. Industrial acnes occur among workers exposed to the following chemicals.

Cutting oils.	Used by machinists.
Crude petroleum.	Occurs among oil-field workers, oil-refinery workers, paraffin pressmen.
Coal-tar	Occurs among makers and distillers of coal-tar
Heavy coal-tar distillates.	Occurs among wood preservers, roofers, road-makers.
Coal-tar pitch.	Used by briquette-makers, conduit-makers, and in electrical insulation.

TABLE I. DIFFERENTIAL DIAGNOSIS OF OCCUPATIONAL ACNES

ACNEFORM LESIONS DUE TO	AGE	COMMON SITE	CLINICAL HISTORY	CLINICAL CHARACTERISTICS	HISTOLOGICAL FEATURES
Acne vulgaris	14–25 yrs. Acne age.	Face. Shoulders. Back. Chest.	Nothing specific no industrial exposure.	Comedones, follicular papules, and pustules, skin greasy and usually associated seborrhoea capitis.	Widely distended follicular orifice filled with keratinous material and sebaceous material. Cocci in keratin plug. Sebaceous glands hypertrophied. Foreign-body granuloma may be present.
Cutting oil, soluble (rare). Crude petroleum, insoluble.	Any age.	Usually on exposed parts. Extensors of forearms and thighs in contact with soiled clothes.	Occupational exposure such as machinists, in oil-fields, oil refineries, and paraffin pressmen.	Folliculites, pustules, furuncles and even carbuncles. Inflammation round and in acne-like lesions. Comedones on fingers, back of hands, forearms, and back of neck.	Comedo formation but inflammatory reaction round hair follicles and in epidermis and throughout cutis is a striking feature No cocci seen
Coal-tar Heavy coal-tar distillates. Coal-tar pitch.	Any age.	Usually on extensor surfaces, arms, thighs and where soiled work clothes touch skin.	Found in makers and distillers of coal-tar in creosoting of wood, in roofing and road workers. Workers such as conduit makers, briquette-makers.	Melanosis, comedones, and small yellowish cysts. Not inflammatory except when scratched and infected.	Melanin in epidermis and in chromatophores below it. Relatively little inflammatory reaction No cocci. Widened follicular openings plugged with keratinous material. Cysts filled with keratinous and some sebaceous material.

TABLE I—continued

ACNEIFORM LESIONS DUE TO	AGE	COMMON SITE	CLINICAL HISTORY	CLINICAL CHARACTERISTICS	HISTOLOGICAL FEATURES
Chloronaphthalenes. Chlordiphenyls. Chlordiphenyl-oxide.	Any age.	Face, back of ears, shoulders, abdomen around navel, groin, genitalia.	Occupational exposure in manufacture of the chemicals for insulating wires and condensers. Electricians using heat and flame-proof wires. Machinists exposed to cutting oil containing chlorinated hydrocarbons.	Comedones not as prominent as straw-coloured cysts. Not inflammatory except when secondarily infected.	Cystic lesions predominate with the absence of cocci in the keratinous material filling widened follicular openings. Otherwise can resemble acne vulgaris but cysts have more keratin than sebaceous material.
Solid chlorbenzols. Solid chlorphenols.	Any age.	Face. Anterior Surface of body	Occupational exposure in chemical workers.	Comedones not prominent. Cysts less prominent than from chloronaphthalenes. There may be an inflammatory allergic dermatitis.	Except for allergic dermatitis essentially that of the chloronaphthalenes.

Solid chlornaphthalenes Chlordiphenyl Chlordiphenyl oxide. Solid chlorbenzols. Solid chlorphenols	Occurs among makers of electrical insulators and electric insulation workers.

The diagnosis of occupational acne presents little difficulty in workers older than 25 years, in whom *in many instances acne vulgaris is not to be considered.* The history of working with any of the above chemicals, the site of the lesions on the arms, neck, behind the ears, abdomen thighs and even the genitals, as well as on the face, is in itself sufficient to make an aetiological diagnosis. The diagnostic criteria for occupational acne *as caused by the various chemicals and acne vulgaris are* shown in Table I published by Schwartz and Peck (1943)

The treatment of occupational acnes consists in expression of comedones, evacuation of cysts and abscesses, and the frequent use of skin cleansers. X-rays *should only be used in special cases* and with caution because the rationale of their use for treating acne vulgaris does not apply to the occupational acnes.

OCCUPATIONAL CANCER OF THE SKIN

Workers with tar soot, pitch, crude petroleum, actinic rays, x-rays, and radium, who develop skin cancers, may claim that it was due to occupational exposure. However in these cases the normal incidence of skin cancers, especially after middle age, must be considered and evaluated against the length and degree of exposure to the carcinogen In addition it should be remembered that occupational cancers appear on the parts exposed to the carcinogen they are often multiple and recurrent they are preceded by pre-cancerous lesions, some of which may be present they appear only after years of occupational exposure to the carcinogen they rarely have metastases.

The occupational origin of a metastasizing squamous-celled epithelioma of the lower lip in a pipe smoker who works with coal-tar is highly questionable. So is a basal-celled epithelioma on the face of a blonde who lives and works in the oil-fields of southern California. The same may be said of skin cancers on the exposed parts of workers over 40 years of age who live and work in the tropics, even though they are exposed to carcinogens other than actinic rays.

The role of contact with arsenic as a cause of occupational cancer is open to debate. To claim that the epithelioma appearing on the face and hands of a blonde middle-aged farmer is due to handling arsenical insecticides is, to say the least, far fetched when his exposure to the sun is considered

Examination by the writer of many hundreds of workers making arsenical insecticides and of smelter workers coming in contact with arsenic trioxide (a waste in the smelting of copper ores) has failed to show any skin cancers, although there were *many cases* of dermatitis and nasal catarrh due to arsenic. The medical records of the factories in which arsenic is handled failed to show skin cancers. The reports of the State Workmen s Compensation boards of the United States of America for the past 10 years were reviewed and failed to show skin cancers

attributed to arsenic, although there were many attributed to coal-tar and petroleum.

The writer has seen several cases of arsenical keratoses, none of which had any other exposure to arsenic except that in all there was a history of having taken Fowler's or Donovan's solution for many years.

TRAUMA AND CANCER

Cancers arising in occupationally incurred scars may be called occupational. Chronic occupational irritation may also be a cause of skin cancer. Slight traumas occur frequently and cancer at the site of the trauma is rare, while malignancy is often erroneously attributed to faintly remembered injuries. In order, therefore, to attempt to prove trauma as the cause of a cancer it must be shown that the affected part was normal before the injury; that the trauma was severe or often repeated at the site where the cancer appeared; that a sufficient interval elapsed after the occurrence of the injury before the cancer appeared; and that a biopsy confirms the diagnosis of cancer.

DERMATOPHYTOSIS IN INDUSTRY

There has been a prevalent idea in the United States of America that an unusually high percentage of workers were affected with fungous infection of the feet, the so-called "athlete's foot", and that these fungous infections were largely spread through the medium of the shower-bath and change-room floors.

It was also believed that the presence of a fungous infection of the feet accompanied by allergic manifestations on the hands, the so-called *id reaction*, predisposed the worker to other allergic dermatitides, thus making the differential diagnosis between the phytids of the hands and occupational dermatitis a frequently occurring problem for the physician.

As a result of studies conducted by the United States Public Health Service in 1943 in 6 industrial plants, when more than 2,100 workers were examined clinically, microscopically and culturally for the presence of fungous disease of the feet and id reactions of the hands, it was shown that about 45 per cent of the workers had fungous infections of the feet and only 3 cases of the 2,123 examined showed an accompanying vesicular or scaling eruption of the hands which could be diagnosed as an id reaction. These figures are no higher than the incidence of fungous infection among the general population in the United States of America.

Pathogenic fungi could not be recovered from the shower-room floors of concrete or pine immediately after several hundred workers with bare feet had walked over them, although under laboratory conditions it was possible to recover *Trichophyton gypseum* from concrete and pine slabs upon which the fungus had been planted.

Other information sought by the studies pertained to the fungistatic and fungicidal properties of antiseptic foot-baths, antiseptic foot-mats, and special copper-impregnated flooring, all of which are highly recommended and marketed by their various manufacturers as being capable of controlling the problem of

contracting and spreading fungous disease in the shower-rooms and change-rooms

It was found that of two large groups studied, one group taking compulsory showers (using a 1 per cent hypochlorite solution for antiseptic foot bath purposes) showed no less incidence of fungous disease of the feet than the comparison group which took no showers and used no foot bath whatsoever In addition, *Trichophyton gypseum* planted on copper impregnated concrete was recovered after 72 hours Many of these prophylactic measures may be efficacious against the fungus under prolonged laboratory conditions, but when applied for practical purposes, it is generally believed by dermatologists that they are inefficient.

As a matter of interest, the Trichophytin sensitivity test performed on a group of workers having allergic dermatitis from trinitrophenylmethylnitramine (Tetryl) and trinitrotoluene (TNT) and compared with the incidence of Trichophytin sensitivity among the whole group studied showed no significant difference (46 and 43 per cent respectively)

These studies have helped towards the conclusion that the logical method for the prevention of dermatophytosis of the feet is through the medium of personal hygiene, namely the wearing of wooden-soled bathing clogs in the shower-rooms and shower baths, the thorough drying of the interdigital spaces and the arches after bathing and when excessive perspiration is present, the using of a foot powder for the purpose of keeping the feet dry

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CHAPTER 13

DERMATOLOGICAL PROBLEMS IN TROPICAL AND SUB TROPICAL AREAS

A. GIRDWOOD FERGUSON

IN considering the problems which face the dermatologist in the tropics and subtropics, due regard must first be paid to the incidence of skin diseases in these parts of the globe. While certain conditions are endemic solely in tropical and subtropical regions, the common diseases of temperate climates are also encountered, and indeed form the bulk of practice in the specialty. Under the climatic conditions of hot countries, these present totally new problems, and in some instances become of relatively serious significance as regards health in comparison to their course, prognosis, and response to treatment in more temperate zones.

A typical survey of skin diseases affecting a white population living under tropical conditions—in point of fact British prisoners of war and internees in Thailand at the close of the recent war—revealed the following disease incidence.

Ringworm (non-tropical) - - - - -	55 per cent
Scabies - - - - - -	6 per cent
Ecthymatous ulcers - - - - -	15 per cent
Miscellaneous diseases (non-tropical) - - - -	17 per cent

The remaining 7 per cent of cases had skin diseases, such as tinea imbricata and cutaneous leishmaniasis, which are indigenous to the tropics. Except in areas in which foci of indigenous disease are present, surveys of diseases existing among native populations have produced, in the writer's experience, a nearly similar result, the incidence of animal parasitic infestations usually being much higher owing to the filthy conditions prevalent in bazaars and villages.

The common diseases of global distribution must then receive more careful consideration than is usually afforded them in considering dermatological practice in the tropics, and this is said without in any way seeking to detract from the great importance to health and life of a thorough knowledge of the conditions peculiarly tropical in their incidence.

MODIFICATIONS PRODUCED BY TROPICAL ENVIRONMENTS UPON THE AETIOLOGY SYMPTOMATOLOGY AND PROGNOSIS OF COMMON SKIN DISEASES

Urticaria

Among the vascular disorders of the skin which are common problems in the tropics, one of the most troublesome is urticaria. Aetiological factors of prime importance, due to geography are heat, light, parasitic infestations of the intestines,

and the exhibition of vaccines and sera essential for the prophylaxis of many of the great killing diseases of hot climates. As in temperate areas, certain foods, drugs, external parasitic invasions and internal foci of bacterial infection must also be kept in view as causal factors, but are of secondary importance in the production of this well-known cutaneous type reaction

Erythema multiforme

The exudative and nodular types of Erythema multiforme are allied conditions which also present fresh causal aspects. Factors in aetiology more commonly encountered in the tropics, are the sulphonamide drugs and emetine iodides in copious use in treatment of the dysenteries and if this is kept in mind the intracta bility of many cases will become patent, and much needless investigation will be obviated

Vesicular and bullous dermatoses

The great group of vesicular and bullous dermatoses presents many troublesome aetiological problems, not the least of which is the fact that tropical climatic conditions provide a variety of animal and vegetable irritants of the skin unknown in colder areas, while retaining most of those more familiar therein The use of photo-sensitizing drugs, for example the sulphonamides and acriflavine, in the treatment of wounds burns, and superficial infected conditions of the skin is also fraught with danger and acute spreading dermatoses due to sensitization to sunlight are common findings, as was noted during the recent war in the East.

From the point of view of course and prognosis, a condition such as prurigo aestivalis, or the allied hydroa vacciniforme, will obviously become a greater hazard to health in countries in which exposure to bright sunlight is almost an everyday matter Further the swift onset of secondary pyococcal infection of originally sterile lesions owing to excessive sweating with its relatively alkaline reaction, which produces a state of the skin surface ideal for the proliferation of pyogenic organisms, is another factor of note in this connexion.

Psoriasis and allied conditions

Those skin diseases which present as their cardinal features scaling and/or lichenification form an interesting study under tropical conditions. Of these, perhaps the most important is psoriasis, which has usually been held in the past to be benefited by life in hot countries The main reason for this supposition was, of course, that many cases were known to be improved by exposure to ultra violet rays and natural sunlight but solar rays in temperate areas and sunlight of tropical intensity are two very different matters. Excessive sweating of the skin in the tropics is a natural sequel of heat and humidity and Crew and Whittle (1938) have shown that sweat absorbs ultra violet light. The result is that, in the tropics, practically nothing but visible light reaches the skin, and any beneficial effects produced by the shorter wave-lengths are eliminated Psoriatic eruptions generally become much worse owing to friction and secondary pyogenic infection, or at best, persist with remission and relapse in the usual manner It is difficult to see how the impression that psoriasis improved, or seldom occurred, under tropical conditions ever gained general currency as the disease is a common one among scantily-clothed native peoples.

Seborrhoeic states

The allied group of diseases known as the seborrhoeic states, which includes seborrhoeic dermatitis, acne vulgaris, and rosacea (all conditions of global distribution), presents features of chronicity and intractability under temperate climatic conditions. In the tropics the diseases are even more of a problem, since the eczematous forms readily become secondarily infected, as also do the acneform eruptions, owing to sweating and the friction of soiled garments. As in the case of psoriasis, and for the same reasons, the acnes do not benefit from tropical sunlight, despite the fact that ultra violet light is one of the main "sheet anchors" in their treatment in temperate zones. In addition, the exhibition of iodides in the treatment of amoebic dysentery very often aggravates a pre-existing constitutional acne as well as superimposing upon it a drug eruption (acne artificialis) of similar nature. The condition known as rosacea is usually considerably aggravated by the heat and humidity of tropical climates, which tend to cause enhanced dilatation of the superficial vessels of the facial skin, and to encourage the appearance of the secondary staphylodermia which is a well-known complicating factor

Lichen planus

Lichen planus, a papular and scaly skin disease in its two most common forms, has never been a great problem whatever its geographical distribution. During World War II, however a closely related condition has been found to occur among troops serving in tropical and subtropical areas, and has been described as almost certainly due to idiosyncrasy to the mepacrine in general use as a malaria prophylactic by Schmitt, Alpins, and Chambers (1945), and also by Nisbet (1945). This eruption, which has been given the name of "tropical lichenoid dermatitis" on account of the acute and exudative features of its early stages, invariably progresses to a hypertrophic lichen planus-like stage and on resolution leaves behind it a most disfiguring massive or reticulate pigmentation of a brown or slaty hue. It must be considered as a new cutaneous hazard among natives and settlers in tropical lands, although the percentage of potential victims appears, from the evidence as yet available, to be low

Lupus erythematosus

Lupus erythematosus, included in this section of cutaneous disorders on account of its scaling propensities, presents a most important problem in the tropics in view of the part played by solar sensitivity in its aetiology and course. It is very well known that this disease often commences after undue exposure to sunlight, and that both ultra violet and natural solar rays aggravate the malady In tropical regions this danger is greatly increased, and conversion from a chronic discoid state to one of acute dissemination and grave illness is often a rapid and frightening event. As a danger to life in the tropics, lupus erythematosus deserves considerable attention.

Exfoliative dermatitis

Exfoliative dermatitis is not a great problem except as regards the very manifest probability of severe secondary pyogenic infection. The course and prognosis may for this reason, be even more difficult to assess than is the case under

and the exhibition of vaccines and sera essential for the prophylaxis of many of the great killing diseases of hot climates. As in temperate areas, certain foods, drugs, external parasitic invasions, and internal foci of bacterial infection must also be kept in view as causal factors, but are of secondary importance in the production of this well known cutaneous type reaction.

Erythema multiforme

The exudative and nodular types of Erythema multiforme are allied conditions which also present fresh causal aspects Factors in aetiology more commonly encountered in the tropics are the sulphonamide drugs and emetine iodides in copious use in treatment of the dysenteries and if this is kept in mind the intractability of many cases will become patent, and much needless investigation will be obviated

Vesicular and bullous dermatoses

The great group of vesicular and bullous dermatoses presents many troublesome aetiological problems, not the least of which is the fact that tropical climatic conditions provide a variety of animal and vegetable irritants of the skin unknown in colder areas, while retaining most of those more familiar therein The use of photo-sensitizing drugs for example the sulphonamides and acriflavine, in the treatment of wounds, burns, and superficial infected conditions of the skin is also fraught with danger and acute spreading dermatoses due to sensitization to sunlight are common findings, as was noted during the recent war in the East.

From the point of view of course and prognosis, a condition such as prurigo aestivalis, or the allied hydroa vacciniforme, will obviously become a greater hazard to health in countries in which exposure to bright sunlight is almost an everyday matter Further the swift onset of secondary pyococcal infection of originally sterile lesions owing to excessive sweating with its relatively alkaline reaction, which produces a state of the skin surface ideal for the proliferation of pyogenic organisms, is another factor of note in this connexion.

Psoriasis and allied conditions

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condition have difficulty in living owing to the complete lack of protective pigment in their skins.

As for the acquired type, problems connected with its onset in the tropics are (1) the propensity of the depigmented areas to react to sunlight with vesicular inflammation in fair-complexioned individuals, and (2) the often considerable psychological upset due to the cosmetic effects of the condition and on account of ignorance of its true nature among native populations, by whom it is often wrongly supposed to be neural leprosy. Acute inflammatory reactions in depigmented parts are more common than used to be supposed and constitute a very real tropical hazard.

Diseases caused by animal parasites

The common animal parasitic infestations are rife in hot countries, owing chiefly to overcrowding, dirt, and indiscriminate cohabitation in native quarters. Certain industries, such as the copra trade, may account for infestations by various species of *Tyroglyphidae* (see p. 195). The main hazard, however, is the relatively speedy onset of secondary pyogenic infection and eczematization which occurs if the diseases are not quickly diagnosed and treated. When cases of scabies and pediculosis are thus complicated in an extensive manner they may present problems in diagnosis, prognosis, and treatment such as to tax the most agile mind.

Fungous Infestations

Fungous infestations of the skin follow in general the course familiar in temperate regions, except that here again climatic conditions in the tropics and subtropics favour complicating pyococcal infection. Tinea capitis of the animal type is prone to occur among predominantly agricultural populations, adults being as frequently affected as children and the infecting agent being usually *Microsporon lanosum*. Tropical climatic conditions favour the viability of the common pathogenic fungi, and copious sweating favours their entrance into the skin. Moderate exposure of the skin to light, and the avoidance of thick footwear and heavy sweat soaked socks appear on the other hand, to have a retarding effect on the onset and spread of such diseases.

It may be noted that an additional risk in the tropics is the now generally accepted depigmentary action of some of the common fungi. Parasitic achromia undoubtedly occurs, particularly among dark-skinned persons, and its appearance is apt to produce much the same effects upon the native mind as the appearance of leucoderma. It should be borne in mind in the differential diagnosis of depigmentary states.

Diseases due to bacterial infection

Diseases due to bacterial infection flourish greatly under tropical conditions, and in general are more difficult to control owing to alkaline sweating and continual re-infection. Ecthymatous ulcers present the usual aetiological factors, as indeed do all the other common organismal conditions, but appear more often to occur spontaneously among young and healthy adults than in more temperate zones. The Klebs-Löffler bacillus has been blamed for this happening, but most cases of ulceration with diphtheritic infection have been found to have been associated with a known case of faucial diphtheria, and the general conclusion would appear

temperate conditions, and this must always be kept in view. If anything, however, chest complications due to chilling seem less common in the tropics owing to higher air temperatures, a finding of some importance on the credit side.

Hypertrophic, atrophic, and pigmentary disorders

Under the heading of hypertrophic, atrophic, and pigmentary disorders many problems arise for the dermatologist. Ichthyosis congenita is a condition which usually causes considerable disturbance to health in view of the associated sweat and sebaceous gland dysfunction. While a small group of mild cases has been found to improve in hot atmospheres owing to over-stimulation of the remaining active glands, the bulk of sufferers from this congenital condition develop symptoms of disturbance of the heat regulating mechanism owing to inability to react to high temperatures with a sufficient flow of sweat. In addition the xerodermatous skin is well known to be prone to develop inflammatory response to minor external irritation and this is as true in tropical as in temperate areas. The sufferer from ichthyosis is, therefore, anything but a good "risk" in hot climates.

Phrynoderma is a hypertrophic disease of the skin which is generally accepted as due, at least in part, to vitamin A deficiency though there is some modern evidence to show that lack of vitamin B_2 may also play a part. It has been accepted in the past as being more common in tropical areas, owing to the deficient dietary of most native peoples and the greater incidence of such bowel diseases as sprue, the dysenteries, and hill diarrhoea, which tend to hinder absorption of fat, and therefore of fat-soluble vitamins. In the writer's experience, despite the opinions of Stannus (1945), there is every reason for continuing to accept this view and to regard the disease as a hazard most likely to be encountered in the tropics. The same is undoubtedly true of most of the other deficiency states which present cutaneous signs, notably pellagra, the skin manifestations of which are now being likened to "crazy paving".

The cutaneous atrophies met with under tropical conditions are exemplified by two conditions which are probably closely related. The first, chronic erythema solare or "sailor's skin", is a disease affecting exposed parts; it usually occurs in persons particularly of blonde complexion and having a tendency to freckling, who have spent many years under extreme climatic conditions. The second, which resembles a precocious form of the first, is the disorder known as xeroderma pigmentosum, which is a disease of childhood. Both occur in individuals who have an abnormal cutaneous response to sunlight, and there has been some evidence to show that the exciting factor is in the short ultra violet wave-bands. Hence these conditions do not constitute a great problem in the tropics except in relatively temperate parts, such as upon the sea or in mountainous areas. They are worthy of note, however, and sufferers are certainly not suited to tropical environments. There is danger to life owing to the development of carcinomatous changes in the affected skin, which, at first erythematous, passes through subsequent stages of pigmentation, telangiectasis, atrophy, and finally tumour formation.

Anomalies of pigmentation include albinism and acquired leucoderma. The first is probably most common among the primitive inhabitants of tropical countries owing to the prevalence of consanguinity in the married state. Sufferers from this

causes of pathological pigmentation are, of course, malaria, and kala azar which must always be remembered in differential diagnosis.

As regards hypertrophies of the skin, one which might be expected to occur frequently is keloid scarring, in view of its apparently high incidence among negroes. This, however has not been the writer's experience, and this is borne out by the findings of Wolfe (1945) who, in a summary of skin diseases occurring among natives of north-east New Guinea, found keloids to comprise only 1·6 per cent of the total. Further the same author noted that large pendulous keloid scars were rare occurrences and small ones the rule.

Many conditions due to animal parasitic infestation are indigenous in tropical and subtropical areas. Examples are cutaneous amoebiasis, ground itch swimmers itch and filariasis.

Craw-craw is an itching condition characterized by multiform lesions. There is still some doubt as to its exact cause, but a variety of filaria is usually suspected. The chief importance of the condition lies in its close resemblance to scabies and in the swiftly complicating pyococcal infection which occurs in neglected cases.

Filariasis is, of course, the chief cause of elephantiasic states in endemic areas, but other very common factors are intermittent pressure and recurrent streptococcal infection of the skin, which cause lymphatic blockage and produce the variety known as elephantiasis nostras. This type of chronic lymphatic inflammation must be kept in mind, as thereby treatment of certain cases of elephantiasis will be greatly simplified. Onchocerciasis of the American type, another filarial condition, has been well described by Goldman (1944). Types of cutaneous reaction associated with the affection have more recently been detailed by Goldman and Ortiz (1946) and form an interesting study in non-specificity being reported as follows.

(1) Reactions associated directly with the onchocerciasis

(a) Subcutaneous nodules.

(b) Dermatitis.

( ) *Mal de morado* or dermatosis pigmentada onchocercosa.

(ii) Localized oedemas (elephantiasis) acute and chronic.

(iii) Forms of lichenification.

(iv) Acute, subacute, and chronic eczematoid dermatitis with or without pyodermas.

(c) Reactions to the bite of a fly of the genus *Simulium*.

(d) Scarring from cutaneous biopsies or excision of nodules.

(e) Dermatitis from therapeutic agents.

(2) Non-related cutaneous conditions in patients with onchocerciasis

This type of filarial infection is, therefore, responsible for much more than classical elephantiasis, and this is equally true of other varieties of filariasis.

Other types of cutaneous worm infestation include the wound-infesting *Muscidae* and the *Oestridae* which are deposited beneath the skin and form furuncle-like lesions which ultimately discharge the larvae. Hypodermiasis (or ox warble disease) is found among herdsmen and shepherds and is due to the very early

to be that infection of existing sores occurs *post hoc.* Spontaneous onset of ecthyma in the healthy adult is not, in the experience of the author a common finding in temperate climes and is still a problem to be solved as regards the tropics. In this connexion also the modern tendency to apply numerous descriptive titles to this simple condition (e.g. veldt, desert, or jungle sore) is to be deplored as tending to cause its identification with differing aetiological entities in most cases indigenous in tropical regions.

Folliculitis and infectious eczematoid dermatitis are conditions extremely common among natives, particularly sepoys wearing something which approximates to European clothing. The disorders in such persons are usually due to the friction upon hair follicles of the unaccustomed sweat-soaked and dusty garments, although another common causal factor is the failure of authorities to provide adequate changes of clothing for members of anti-malaria units who are engaged in spraying oil upon the breeding places of mosquitoes.

The so-called pemphigus contagiosus or tropical pemphigus is, of course, merely bullous impetigo of staphylococcal origin. It commonly complicates prickly heat, especially if the latter condition is neglected or inadequately treated.

Diseases of the appendages

The common conditions of the group known as diseases of the appendages behave in general as in temperate areas, though symptomatic hyperidrosis is probably more often encountered owing to the high incidence of febrile states and the high air temperatures in tropical lands. The idiopathic type of hyperidrosis may commonly result from psychosomatic causes referable to dislike of limited company home-sickness and depression as a result of repeated attacks of tropical diseases such as malaria In this connexion the writer is of the opinion that numerous examples of cheiropompholyx and podopompholyx, occurring in persons living and working in the tropics and usually considered in the past to be of fungous or infective origin, are in fact due to psychosomatic disorders.

SKIN DISEASES PECULIAR TO TROPICAL AND SUBTROPICAL AREAS

Among bullous and vesicular dermatoses, those peculiar to the tropics are for the most part in the class of dermatitis and eczema produced by external irritation. A common example is the dermatitis produced by exposure to the oil of the cashew nut, a solution of which is much used by tailors and laundrymen to make ink for marking garments Acute localized irritation of the skin in the region of the collar band posteriorly a favourite site of the dhobie mark is a useful pointer to the vegetable aetiology of such a condition Various and numerous plants, fruits, and woods, indigenous in the tropics, produce eruptions of a similar nature.

Among pigmentary disorders one most common in, and probably more or less peculiar to tropical climates is the yellow staining of the skin which follows the ingestion of large numbers of oranges or squashes. The condition is due to carotenaemia and is known as carotenoid pigmentation A useful differentiating fact in distinguishing the condition from other pigmentary anomalies is the primary involvement of the skin of the palms and soles, the conjunctivae being only rarely affected and if so only in the later stages of the disease process. Other common

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flies caught in these burrows showed flagellates, whereas other wild flies caught revealed only 3.5 per cent. As regards the gerbilles, 30 per cent of wild species (most commonly *Rhombomys opimus*) showed lesions of leishmanial type, while laboratory animals proved definitely susceptible to *L. tropica*.

From the clinical aspect, Kojevnikov has established two forms of the disease depending apparently upon distribution of the populace affected in either urban or country areas, and corresponding closely in description to oriental sore and espundic chancre respectively. He tabulates his findings as follows.

	L. TARDE EXULCERANS	*L. CITO NECROTISANS*
Definition	Dry	Moist lesions with early ulceration
Synonyms	Ashkhabad or Kokand sore	Pendeh or Sart sore
Incubation period	Long (2–6–12 months)	Short (1–6 weeks)
Course	Chronic, unbroken dry papules, ulceration retarded, persists up to year	Acute moist lesions, ulceration in 5–10 days, duration less than 6 months
Lymphangitis	Rare (10 per cent)	Common (70 per cent)
Parasites	Numerous	Few
Virulence for mice	Low	High
Distribution	Urban	Rural
Seasonal	Perennial	Aestivo-autumnal

The sole disturbing factor here is the addition of new district names, such as Kokand, which may become added to an already lengthy list including Biskra, Baghdad, Delhi, and others. It would be better if such synonyms were entirely eliminated from text-book descriptions of this disease, as they serve merely to confuse the issue.

The allied condition, granuloma inguinale, would now appear to have been accepted to be a venereal problem.

Spirochaetal Infections

Of diseases due to spirochaetal infection endemic in the tropics, those of major importance (besides syphilis) are yaws and pinta. *Wit kop* a crusted condition of the scalp met with among natives of South Africa, has apparently remained accepted as of syphilitic origin.

Yaws, endemic chiefly in North and West Africa, Asia, Australia, and the West Indies, is still thought by some clinicians to be a tropical variety of syphilis. In this connexion, a recent report by Findlay and Willcox (1945) is of considerable interest. It records a human experiment in which an individual recently suffering from active tertiary yaws was infected with syphilis in an endeavour to ascertain to what extent the immunity conferred by yaws protects against syphilis, a question not so far clearly elucidated by animal investigations. The investigators conclude that in this particular individual no immunity to *Spirochaeta pallida* is conferred by the presence of long-standing yaws.

It is now generally accepted that mal del pinta, a disease notably endemic in tropical America, is of spirochaetal origin. It is of interest in that it must be remembered as probably the commonest cause of cicatricial alopecia in the tropical areas in which it is indigenous.

larva of one of the genus *Hypoderma* which burrows into the tissues or is ingested, and ultimately gives rise to hypodermal and corial swellings. Larva migrans or creeping eruption is usually caused by either nematode worms such as *Ancylostoma duodenale* or by the larva of the bot fly genus *Gastrophilus* It is widely distributed throughout the tropics, the same condition being given the name of sandworm disease in Natal. The best known local condition produced by ancylostomes is, however *mazamorro* or ground itch a papulo-vesicular dermatitis of the feet and ankles which is a common industrial disease among rice-field coffee-plantation, and banana plantation workers of tropical climates.

Swimmers itch is the common urticarial and papulo-pustular eruption due to irritation by the cercariae of schistosomes, but Black (1945) has drawn attention to a rarer type of eruption involving actual deposition of the eggs of *S haematobium* in the tissues. The disorder is described as commencing during treatment of developed schistosomiasis with Stibophen and is said to take the form of grouped shotty pink papules, which later become nodular of a violet colour and apically pustular and slowly heal with slight induration The lesions yielded ova in two out of four cases The sites of election in the cases described were nipple, umbilicus, and more commonly perineum, scrotum sacral region, and root of penis. This type of schistosome dermatitis is not unknown but has received only scanty attention in the literature.

As regards the above it is interesting to note that Blacklock (1945) has recently commented upon the acquired immunity which gradually develops in man to metazoan parasitic infestations.

The eruptions caused by mites of the *Tyroglyphus* family have already been referred to above. Straw or barley itch is a varicelliform eruption due to infestation by *Pediculoides ventricosus* and is often an occupational condition among handlers of grain straw cotton, rice, and jute in the tropics. The chief importance of this disease rests in its close resemblance to chicken-pox and, in some cases to smallpox. From the latter the main points of distinction are the mild systemic upset and the lack of involvement of the face and mucous membranes Chigger flea infestation is a condition so well known as scarcely to merit further description here.

Cutaneous leishmaniasis

Cutaneous leishmaniasis is commonly accepted as existing in two distinct forms namely oriental sore and South American dermal leishmaniasis, both due to species of the protozoon leishmania, probably *Leishmania tropica* and the main difference being that in the American variety (espundia) there is a greater tendency to local lymphatic involvement.

Recent Russian work has been reviewed by Hoare (1944) and summarized by Manson-Bahr (1945) and seems to suggest that the type of lesion produced depends rather upon local geography than upon any difference in race or the resistance of the individual Latyshev and Kriukova Kojevnikov and point out that, in Middle Asia endemic foci are to be found in urban areas and also in desert spaces. In the latter the sand fly vectors breed almost exclusively in the burrows of wild rodents (gerbilles and marmots) which live in the sand and 6–35 per cent of female

invading organisms by the tissues of the host, spontaneous remission and cure commonly occurring. As regards histopathology there is here a cuffing of corial vessels and hair follicles by round cells which also invade the sheaths of the cutaneous nerves. Macrophages next appear and become epithelioid cells, which form a tubercle and fix the few bacilli present.

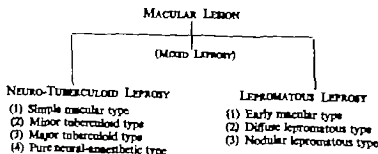
(2) Minor tuberculoid type, which is a further stage of the above, the lesions being often single and showing the same well-defined edges, now raised, erythematous and tending to show slight infiltration. There is anaesthesia or hyperaesthesia in the areas of skin involved, and nerve involvement remains as above, the great auricular ulnar and peroneal nerves being usually first affected. Here the pathology differs from the above only in that the epithelioid cell reaction is more marked and giant cells have made their appearance.

(3) Major tuberculoid type this, the third stage of the above, presents large plaque-like and very anaesthetic lesions with raised, thickened, and pebbled edges. The skin nerves are markedly enlarged and may be abscessed. The pathology is as in type (2), but shows an even more marked tissue reaction.

(4) Pure neural-anaesthetic type, in which there is an attack by the bacilli entirely upon the nerve sheaths and fibrils. The nerves are greatly thickened and the symptomatology is that of a peripheral neuritis, the only skin lesions being of trophic nature. As to pathology the defence reaction, composed entirely of connective tissue cells, occurs entirely within and around the nerves, with complete destruction of the invading organisms, but also irreparable damage to the nerves themselves.

SCHEMATIC CLASSIFICATION OF LEPROSY

(After R. G. Cochrane)



Lepromatous leprosy is subdivided under the following heads.

(1) The early macular variety in which the lesions are smaller than the simple macules of the neuro-tuberculoid type, are usually multiple and symmetrically distributed, especially upon the face and limbs, and have

Parasitic diseases

Diseases due to vegetable parasites are, in a few instances, found only in warm climates and may feasibly be divided into fungous and bacterial groupings.

Tinea imbricata, common in the Far East and in Polynesia, has to be distinguished from simple tinea corporis of severe and widespread type. On a dark skin its watered silk appearance is diagnostic, and in white patients, the multiple concentric ringing of the lesions together with their considerable induration, unusual in simple ringworms should serve to establish diagnosis. There is occasional difficulty in cases in which the disease becomes generalized, when it may present an extraordinary resemblance to congenital ichthyosis and the rare generalized infiltrative type of nodular (lepromatous) leprosy

The diseases severally known as leptothrix (trichomycosis) trichinocardiasis, nocardiosis cutis, and black hairy tongue (one type) are in the writer's opinion all variants of one disease, due to infestation by the actinomycetic fungus known as *Nocardia tenuis* in symbiosis with certain chromoblastic organisms. This has been postulated by Castellani and others in the past, but has not been widely accepted as yet, so far as is known.

Mycetoma remains a problem as always and a condition of great painfulness and chronicity to the hapless sufferer Piedra is a fungous disease of the scalp hair (that of the eyebrows, eyelashes, and beard is also sometimes affected), which is caused by the *Trichosporon giganteum* It is probably encouraged in its infestation by the native habit of dressing the head with sweet oil and must be distinguished carefully from other nodose conditions of the hair (e.g. trichorrexis nodosa) which are of non-fungous origin

Leprosy

Of bacterial diseases indigenous to the tropics and subtropics, leprosy is by far the greatest problem There is considerable confusion as to arrangement and nomenclature of the various types and subtypes of this disease, a thorough understanding of which must make for greater accuracy in prognosis and measures to be taken in dealing with individual cases. R G Cochrane, of Vellore College, Madras Presidency India in a personal communication (1945) to the writer lays down a clear-cut outline of the types above-mentioned, based upon pathological as well as upon clinical findings recently (1947) he has published his views.

According to Cochrane, the initial lesion is usually a macule in all varieties, later passing into either neuro-tuberculoid leprosy or lepromatous leprosy As regards the first type, which corresponds to the maculo-anaesthetic leprosy of earlier workers, there is further subdivision as follows.

(1) Simple macular type in which the lesions are hypopigmented macular spots with very sharply demarcated edges, usually distributed on the skin of the extensor limb surfaces, buttocks, and scapular regions, and less often upon that of the face. There may be associated nerve thickenings and slight anaesthesia of the skin usually in the ulnar and peroneal areas. The lesions themselves may or may not show slight sensory disturbance, heat sensation being often first lost. They may be single or multiple, and this type is the best example of the overcoming of the

invading organisms by the tissues of the host, spontaneous remission and cure commonly occurring. As regards histopathology there is here a cuffing of corial vessels and hair follicles by round cells which also invade the sheaths of the cutaneous nerves. Macrophages next appear and become epithelioid cells, which form a tubercle and fix the few bacilli present.

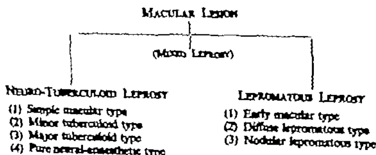
(2) Minor tuberculoid type which is a further stage of the above, the lesions being often single and showing the same well-defined edges, now raised, erythematous and tending to show slight infiltration. There is anaesthesia or hyperaesthesia in the areas of skin involved, and nerve involvement remains as above, the great auricular ulnar and peroneal nerves being usually first affected. Here the pathology differs from the above only in that the epithelioid cell reaction is more marked and giant cells have made their appearance.

(3) Major tuberculoid type this, the third stage of the above presents large plaque-like and very anaesthetic lesions with raised, thickened, and pebbled edges. The skin nerves are markedly enlarged and may be abscessed. The pathology is as in type (2), but shows an even more marked tissue reaction.

(4) Pure neural-anaesthetic type, in which there is an attack by the bacilli entirely upon the nerve sheaths and fibrils. The nerves are greatly thickened and the symptomatology is that of a peripheral neuritis, the only skin lesions being of trophic nature. As to pathology the defence reaction, composed entirely of connective tissue cells, occurs entirely within and around the nerves, with complete destruction of the invading organism, but also irreparable damage to the nerves themselves.

SCHEMATIC CLASSIFICATION OF LEPROSY

(After R. G. Cochrane)



Lepromatous leprosy is subdivided under the following heads.

(1) The early macular variety in which the lesions are smaller than the simple macules of the neuro-tuberculoid type, are usually multiple and symmetrically distributed, especially upon the face and limbs, and have

ill-defined edges. *There is seldom any anaesthesia in the areas of skin affected and on biopsy bacilli are numerous.* As regards pathology there is here an early round-celled infiltration which, however is not focal and does not show a *great deal of epithelioid cell formation.* Macrophages appear but become large and foamy ingest bacilli, and are known as lepra cells. The tissue response is poor in comparison with that of the early neuro-tuberculoid type and the bacilli are able to multiply and disseminate in consequence.

(2) Diffuse lepromatous form which is rare but apparently more common in Southern India than *elsewhere There are no distinct or discrete lesions,* and the entire skin of the body is in a state of infiltration, organisms being obtainable in quantity in smears taken from almost any area. There is little, if any interference with sensation.

(3) Nodular lepromatous type, which presents the typical tumour-like swellings most marked upon the face and limbs. There is no interference *with sensation The pathological findings are of a massive* non focal granulomatous tissue reaction, organisms being numerous and actively multiplying.

Cochrane admits the existence of a third main form of *leprosy* namely the intermediate type, which presents a mixed neuro-tuberculoid and lepromatous picture but is of the opinion that about 70 per cent of these become ultimately *lepromatous*

As regards diagnosis, apart from the clinical picture, a positive smear is diagnostic, but positive biopsy findings are absolutely distinctive. This is especially true in the neuro-tuberculoid forms in which the obtaining of negative smears is the rule A biopsy must be deep in order to pick up nerve trunks in the hypoderm, as the pathology of neuro-tuberculoid leprosy closely resembles that of Boeck's *sarcoidosis apart from the involvement of nerves*

From the point of view of prognosis Cochrane is of the opinion that many neuro-tuberculoid cases ultimately heal spontaneously and therefore that, apart from the pure neural anaesthetic form *in which the tissue reaction destroys nerve* fibrils and leaves permanent ill effects, the outlook in this type is good. The reason for this is that there is here an adequate tissue defence reaction which prevents *general bacillaemia.* The *outlook in* lepromatous cases and in the bulk of intermediate examples is on the other hand very poor in view of the attendant generalized tissue infection Neuro-tuberculoid cases are *not infectious,* while lepromatous cases are extremely so

Aetiology is now a question which has been partly settled on a sound basis as there is no doubt as to the causal organism while *it is also generally accepted that* the disease is only contracted by contact with an open (i.e. lepromatous) case and that in 70 per cent of patients leprosy develops before they reach the age of 25 years. *The route of infection is, however still not definitely known* though the bacilli have been found capable of entering traumatized skin Cochrane is, however inclined to incriminate the nasal mucosa as *the most likely route in the* majority of cases. A racial immunity is thought generally to exist as regards the

percentage of open cases, as there is no doubt that lepromatous cases are most often encountered among the inhabitants of cooler zones.

The importance of the above as regards case management and prognostic accuracy will be recognized.

Tropical ulcer

Tropical ulcer is another condition of considerable importance and one which causes a high sickness rate. Analogous to the Aden and Malabar ulcer and Naga sore of older text books, which delighted in district names for what is in fact a single entity it is generally accepted as being caused by infection of abrasions by Vincent s organisms. A sloughing and phagedaenic process which usually affects the feet and legs, it presents a problem in treatment of great difficulty under tropical conditions.

Diseases of the appendages

Diseases of the appendages met with in the tropics and subtropics as indigenous states are few in number and only one is of outstanding importance (prickly heat) apart from those diseases of the hair which have been already mentioned.

Alopecia marginalis traumatica deserves consideration, however as a condition of indigenous nature, occurring as it does mainly among natives of Polynesia, South America, and Japan, who wear their hair frizzed and combed severely upward from the margins, or who attempt to dress hair long untended, in European styles. Small patches of marginal alopecia are common owing to this continual, and in some cases unaccustomed, trauma in hair toilet, and have to be distinguished from baldness due to organismal and other causes.

Prickly heat

The condition known as prickly heat remains a scourge in tropical climates, particularly where humidity is high. It appears to be most common among white populations and to occur most frequently and with greatest severity in individuals of a florid complexion and of obese tendency though brunettes and sparely-built persons are by no means immune. Heavy clothing is an aggravating factor as is also a tendency to hyperidrosis, but beyond this the aetiology is obscure.

Fay and Sussman (1945) have made a study of 46 officers serving in one of H.M Australian ships during a period of 6 days and nights of prolonged action, when this ship was within 4 degrees of the equator A number of simple variable factors were studied, and an attempt was made to postulate their effects upon individual susceptibility to prickly heat. The observations are summarized as follows.

(1) Factors which increase the liability of a person to develop prickly heat are (*a*) age over 30 years, (*b*) fair skin, (*c*) nervous temperament, (*d*) large salt intake, (*e*) working and sleeping below decks, (*f*) high temperatures, (*g*) long working hours, (*h*) battle dress or poorly ventilated clothing, and (*i*) perhaps the fact of belonging to blood group O (IV).

(2) Factors which reduce the liability of a person to develop the disease are (*a*) age below 30 years, (*b*) previous sun tan, (*c*) loose clothing, (*d*) working and sleeping in the open air (*e*) low temperatures of places of work, and (*f*) perhaps the fact of belonging to blood group A (II).

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(3) Factors having no effect on the incidence of prickly heat are (*a*) weight, (*b*) sweat reaction (*c*) wearing of open-necked shirts, and (*d*) effects of sun on subject s skin

(4) Factors giving inconclusive results are (*a*) type of work, (*b*) humidity and (*c*) brand of soap used

These various factors do not seem to be a cause in themselves, but when present, affect a susceptible person as indicated. The disease seems to be more constitutional than due to any one factor in particular

There is little consolation in so controversial a subject, as the above observations may be said to cover most if not all of the modern views upon the matter

GENERAL REVIEW OF THE INCIDENCE OF SKIN DISEASES AMONG NATIVE PEOPLES

The writer has formed certain general impressions as regards disease incidence according to race in those parts of the tropics in which he has sojourned, and puts forward the following as his personal views.

With regard to India Ceylon, and Burma the inhabitant of the northern territories (i e. Sikh Pathan and Gurkha) suffers chiefly from indigenous diseases such as leprosy and leishmaniasis. In contradistinction to this the Burmese and peoples of Dravidian stock (i.e Mahrathas, Madrasis, Sinhalese, and Tamils) seem prone to develop bacterial and fungous diseases on a large scale in addition to indigenous conditions The much more humid and warm climates in which the latter live are, however the chief cause of the difference as it is found in general that the more enervating the climate, the greater the incidence of diseases of filth.

The *fellahin* of Egypt exhibit much the same disease incidence as do the Dravidian peoples but African Negroes appear on the other hand, to suffer mainly from diseases peculiar to their own home environments, particularly yaws and leprosy In this connexion however it may be said that Africans were only observed by the writer as soldiers in a foreign land in which they mixed little with the civilian population, and then not under their home conditions.

PROBLEMS OF TREATMENT

These may be considered under two main heads, prophylactic and curative. Preventive treatment should begin with an attempt to institute and extend a system of social medicine.

Social measures

As Kauntze (1946) has said, those who have had little experience of tropical climates find considerable difficulty in envisaging the great differences which exist between the social conditions of such areas and those of temperate countries. He considers these differences to be mainly due to the general lack of education and the poor social economy and to lassitude the latter being partly attributable to climate and the ravages of endemic disease, which generally obtain in tropical regions.

An attempt should, therefore, be made to improve the standards of living among native populations, particularly in urban areas, and with particular reference to water supply sanitation, overcrowding, and diet. As regards the first three of these the problems are clear

With regard to the question of diet, religion in many lands decrees that only certain types of food can be consumed by true believers, while, on the other hand, centuries of experience in the struggle against Nature have taught the native which crops he can most easily grow It does not follow however that the type of diet thus made available is the most suitable for health requirements, and in point of fact this seldom is so. An attempt must therefore be made to put aside centuries of tradition and religious scruples in the interests of communal health, as only thus can deficiency diseases, including those presenting cutaneous symptomatology be controlled and, it may be, eradicated.

There must be, in addition, careful selection and training of medical personnel, both native and European, to deal with cutaneous disease prevention, which should be made an important part of the equipment of doctors and nurses who intend to work in tropical areas. Instructional courses directed towards this end should be instituted in the training schools of tropical medicine and hygiene all over the world, and in this connexion it is with keen interest that the writer has noted the pioneer work of the Mexican Society of Dermatology in co-operation with the Faculty of Medicine of the University of Mexico, which last year held a course in tropical dermatology which was attended by a large number of physicians from the United States of America. Regular courses of lectures and demonstrations, such as those conducted for army specialists during the recent war on the subject of leprosy by Dr R. G. Cochrane at Vellore and Saidapet (Madras), are also required, and facilities should be extended as widely as possible.

It should, of course, be emphasized that it is upon the general practitioner that the bulk of the routine work concerning prevention of disease should and will fall. Those practitioners who are to work in tropical areas must, therefore, form the main body of candidates for the special training referred to above but it is equally important that they should be supported by an adequate staff of dermatological specialists and hygiene officers who have received an even more intensive preparation in the field of tropical dermatology Nurses should be similarly equipped, and numerous old-fashioned ideas anent the unsuitability of female staffing of dermatological departments must be eradicated from the minds of medical authorities (in whose minds they still appear in many cases to be firmly rooted)

As Kauntze has also suggested, areas should be selected for campaigns against preventable diseases, among which skin disorders should, in the opinion of the writer be given important consideration. Teams of the specially trained men and women considered above should be allocated to such tasks, their numbers depending upon the size of the area to be dealt with. Preventable disease would be attacked, and the local permanent medical staff trained at the same time in the methods by which it could be excluded in the future. When the area had been cleaned up, the team would move to a fresh field, leaving a cadre of the permanent and now better equipped staff to maintain the new improvements.

General preventive measures

Much sick wastage due to recurrent skin disease among white populations can obviously be avoided, if individuals suffering from conditions known to be adversely affected by sojourn in tropical climates are either advised against going to such areas or are specially dealt with if it is impossible to stop their going. Thus individuals known to be subject to severe ichthyosis, lupus erythematosus, prurigo aestivalis seborrhoeic dermatitis acne vulgaris, leucoderma, psoriasis, and prickly heat are dermatological bad bargains and should, if possible, not be accepted for or at least should be advised against, tropical service. Blonde or red-haired persons must also be viewed with doubt as candidates for posts in hot climates

If encountered in tropical practice, attempts should be made to place the subjects referred to above in relatively temperate areas such as hill stations, where conditions favour the well-being of their skins, and, in the case of psoriasis and acne, some benefit may even be expected from ultra violet light. Failing this, every effort should be made to induce them to return to work in cooler climates.

In white and native populations alike, the general preventive measures undertaken against the development of parasitic bowel disease should serve to obviate urticaria and other erythematous eruptions due to such causes.

Arrangements directed towards the cooling of houses and offices, such as the provision of a system of exhaust fans and the insulation of domestic sources of heat production can and will do a great deal towards the prevention of heat urticarias hyperidrosis, and prickly heat

The use of photosensitizing drugs in the treatment of superficial infective conditions should be avoided sulphonamides and acriflavine are common causes of widespread photodermatitis superimposed upon an original disease process of relative insignificance. In this connexion also the use of shaving and toilet preparations containing a sulphonamide drug should be prohibited, and ladies should be warned against the application of toilet waters containing essential oils which may react with sunlight to cause unsightly pigmentation of exposed areas.

Local applications which are efficient in temperate zones may require considerable modification under tropical conditions. The use of ointments and creams is attended with the risk of skin maceration and even in the treatment of dry and scaly states they usually have to be discarded in favour of water in-oil emulsions, paints and lotions. It may be said in general, that topical therapy in the tropics should be restricted to the use of lotions, paints, sprays, and the new emulsifying agents.

Specific preventive measures

Dichlor-diphenyl trichlorethane (D D T) should be used on a large scale in bazaars and native houses in order to cut down insect parasitic infestations among the populace, and properly controlled measures of this nature will certainly reduce the incidence of the infective dermatoses, such as impetigo ecthyma and infectious eczematoid dermatitis. Prompt diagnosis and curative treatment of animal parasitic conditions is another useful prophylactic measure against the development of pyogenic infections of the skin.

The common folliculitis due to oil-soaked clothing has already been referred to (p. 280). It can very easily be prevented by insistence upon an off-duty change into fresh and clean garments.

Ringworm of the body may be reduced in incidence to a considerable extent, by exposure of the skin for a few hours daily to the rays of the morning sun. Another measure which was suggested during World War II was the prophylactic painting once weekly of the skin of the trunk and limbs with a weak solution (0·01 per cent) of strong tincture of iodine.

Foot ringworm is relatively uncommon among the barefooted or sandalled natives, and white populations can be spared the continual annoyance of this disease by discarding closely-fitting footwear and socks during the heat of the day. There is no doubt that the retained and relatively alkaline sweat present in socks and heavy shoes forms an ideal nidus for the culture of *Trichophyta* and *Epidermophyta*. Care of the feet is another item of importance, and nightly application of a dusting powder after the bath is recommended. The powder should contain 25 per cent of boric acid.

In view of the recent Russian work on leishmaniasis, a campaign should be directed against the animal hosts (gerbilles and tree rats) of the causal flagellates, as there seems to be little doubt that the disease is a zoonosis. The introduction of D.D.T. should go a long way towards disposing of the fly vector. The simuliids and culicine mosquitoes which carry filarial larvae can, it is expected, be considerably reduced in numbers by the use of the same modern insecticide. It is also hoped that certain itching dermatoses due to mites, such as copra itch, may in future be largely prevented by the recently developed repellants dibutyl and dimethyl phthalate.

It is now generally accepted that individuals presenting the simple macular and other types of neuro-tuberculoid leprosy are not in any way infectious, and so can mix with their fellows and proceed with their ordinary vacations without let or hindrance. Cochrane has pointed out that segregation in leprosaria of the infectious "open" cases has never been, and never can be, a success in view of the shattering of family life which is inseparable from such a measure. His solution is to allow the infectious cases to mix freely by day with their fellows and families (even the susceptible children), segregating them only at night in special quarters set apart in their own villages or towns. He justifies this by his belief that infection is due in almost all cases to intimate contact such as occurs when sleeping in the same bed or room as an infectious patient. By this method, family life is upset little; the patients are happy and contented, cases can be treated with ease and defaulting during treatment is greatly reduced. In addition, Cochrane claims that the numbers of fresh infections have been greatly curtailed in areas in which this system of simple night-segregation has been in operation. The scheme is certainly the most hopeful as yet suggested in the long history of effort to stamp out this scourge of the tropics.

As regards the prevention of tropical ulceration, prompt application of simple antiseptics such as iodine or Friar's balsam to all minor cuts, abrasions, and stings is of the utmost importance. When it is remembered that the loss of a limb is

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not an uncommon sequel to these minor injuries, simple first aid to the skin in the tropics will not seem so unnecessary as it might otherwise appear

There have been several notable advances in curative treatment during the last decade. The sulphonamide drugs carefully used, have been of immeasurable benefit in the swift clearing of pyococcal infection but careless use coupled with the photosensitizing properties of the group, make large-scale employment of these fraught with danger in sunny climates Furthermore, these substances have failed in the treatment of such indigenous diseases as leishmaniasis, mycetoma, and leprosy in which it had been hoped that they might prove helpful.

The introduction of penicillin has, however provided a safer answer to the control of pyogenic disease and its use marks a real advance in both topical and internal medication of infected conditions and tropical ulcers. As regards treatment of indigenous disorders, however it has proved of little more use than the sulphonamide compounds

The allied antibiotic substance, streptomycin now under clinical trial in the United States of America, and shortly to be available for limited trials in Great Britain, will it is hoped prove to be a further potent weapon in the armamentarium of the dermatologist in the tropics. In view of the encouraging results obtained by its use in tuberculosis, it is possible that it may prove of assistance in the treatment of leprosy A small number of cases are already under treatment and results are being eagerly awaited

It is thus clear that many problems confront both the general practitioner and the specialist in the management of skin diseases in tropical climates. This important branch of medicine has been too much neglected in the past in the training of medical men and women destined for posts abroad and it should be realized that a thorough knowledge of cutaneous disorders is a major part of tropical practice.

It is the writer's opinion that the most notable problems are to be found in the field of preventive treatment. This is however not to say that questions of cure are to take a minor place in modern schemes of action in the matter Research in this latter field must proceed actively hand in-hand with that in preventive medicine fully exploiting all the resources of science and nature alike in the fight against skin illness in tropical and subtropical lands.

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Causal agents

Necrobiotic processes may be associated with various infiltrations. Thus, necrotic or dystrophic calcification may be supposed to be due to the deposition of calcium salts in tissues in which necrobiosis or necrosis is present.

As is stated at the commencement, we are here concerned with necrobiotic processes, atrophies, and scleroses in the skin and subcutaneous tissue of uncertain causation rather than with those due to known infective agents and toxins. We have also to consider infiltrations and accumulations in the skin and subcutaneous tissue—usually more or less disseminated, nodular or focal—consisting of calcium salts, lipoids, amyloid material, mucin, etc.—no matter whether such infiltrations and accumulations are apparently primary or are associated with and probably more or less secondary to necrobiotic processes.

It is now acknowledged that Atophan (cinchophen) has sometimes caused acute atrophy (necrosis) of the glandular cells (the parenchyma) of the liver but I feel certain that, in one case which I have seen, a large cirrhotic liver (' hypertrophic cirrhosis ') in an individual with advanced crippling rheumatoid arthritis resulted from the use of that drug, the different result in different cases depending upon the balance between the direct effect of the toxic *agent* and the *reaction* on the part of the tissues.

NECROBIOSES, ATROPHIES, AND SCLEROSES

Ulcers

It cannot be denied that certain individuals have a peculiar (inborn or acquired) constitutional tendency to the formation of ulcers on the skin—especially on the lower limbs—without obvious cause, apart from ordinary pressure, rubbing, or common low-grade infections. To such leg-ulcers, patients with sphaerocytal chronic acholuric jaundice and sickle-celled (drepanocytal) anaemias, as well as patients with some other chronic splenomegalies, are particularly prone. Gänsslen (1925) refers to a sphaerocytal case in which a chronic leg-ulcer refused to heal under any treatment till splenectomy was performed, after which healing was complete in eight days.

Weber, Rast, and Lutterotti (1930) recorded a case of chronic intractable leg-ulcer in a young Englishman, aged 23 years, in whom a cause could not be found, except some limited thrombo-angiitis obliterans. He had been accustomed to smoke about 12 cigarettes daily since the age of 16. The patient's father had suffered from chronic ulcers on both legs before his death at 66 years of age. There certainly is constitutional tendency to ulcus cruris in some families. My colleague, Mr A. Compton, in 1935 had an Englishman, aged 55 years, under his care with cancer in a chronic ulcer of the right leg. An elder brother, the mother and the mother's mother all suffered from ulcus cruris.

Chronic necrobiotic tendency

The late Sir James Galloway used to speak of a constitutional circulatory disorder with tendency to cutaneous redness and necrotic changes (Galloway, 1902a and b).

In 1902 he described the case of a young unmarried woman, aged 26, who first came under his observation in 1897 at the Charing Cross Hospital at the age of 21. He demonstrated her case at the Dermatological Society of London on 12th January 1898. She sought advice on account of the redness of her skin and the scaly condition

CHAPTER 14

NECROBIOSES ATROPHIES SCLEROSES INFILTRATIONS AND ACCUMULATIONS IN THE SKIN AND SUBCUTANEOUS TISSUE

F PARKES WEBER

I SHALL refer as far as possible only to conditions of which the exact cause is unknown or uncertain but here and there, in order to make the whole position more intelligible, I shall not be able to avoid alluding to cases of relatively known causation

I have used the word infiltration to include not only infiltration and deposition of substances carried to the cells and tissues by the blood, but also accumulation and storage of substances due to faulty intra-cellular metabolism.

I shall go very little into details of well-known syndromes and conditions, which are referred to chiefly for purposes of classification and to make the landscape of the subject clear There is always the danger of the tree hiding the forest

Necrobiosis

Necrobiosis (*νεκρός* a dead body and *βίωσις* living), may be variously defined as follows

(1) Gradual death of a part in consequence of degenerative or retrograde processes as opposed to sudden death or necrosis.

(2) Cellular death or necrocytosis (*νεκρός* and *κύτος* a cell) contrasted with tissue death or gangrene.

(3) The following is preferable however from the present point of view what goes on in a part when a degenerative necrotic process is opposed by a vital reactionary process towards repair or regeneration In the early stages recovery may take place and sero-cellular effusions may be completely re-absorbed. This doubtless generally happens in the subcutaneous nodules of acute rheumatism and with some of the nodules associated with rheumatoid arthritis. In other cases only partial recovery takes place, as when, in the chronic necrobiotic nodules of the rheumatoid arthritis type, necrotic foci become surrounded by reactionary fibroblastic limiting zones More or less similar conditions are present in various parts of the body when tuberculous, syphilitic, and other infective granulomatous foci are opposed and surrounded by limiting reactionary fibroblastic zones leading to tuberculous and syphilitic fibrotic lesions. Parkes Weber's paper (1920) on chronic fibroid syphilomata of the legs was apparently the first to draw attention to that particular condition A similar fibrotic reaction towards toxic necrobiotic and ischaemic processes accounts for the changes in both so-called hypertrophic and atrophic types of hepatic cirrhosis and in chronic renal fibroses the size of the organ and degree of sclerosis depending upon the extent of the reactionary process—chiefly of the fibrous elements—that has taken place.

Causal agents

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of her head Her mother s father and her father s mother both died from disease of the heart Her father was alive, suffering from symptoms suggesting tabes dorsalis or general paralysis Her brothers and sisters were alive and well, and inclined to be thin rather than fat When aged 14 she had an attack thought to be scarlet fever and after her convalescence, when she was about 15 her mother noticed that her face was blue and swollen She developed severe headaches accompanied by temporary disturbance of vision. On admission to hospital in 1897 she was fat and of average height. Her cheeks were congested, dusty-red, at times almost cyanotic. The skin of her whole body was congested, having a reddish-purple tint where it is usually white There was oedema of the legs and feet. The breasts were large and pendulous and the areolae congested. There were patches of seborrhoeic dermatitis in several places. The pulse rate averaged about 140 Blood count erythrocytes 6,120 100 leucocytes 60 000 There was polycythaemia. Treatment by prolonged rest made her feel more comfortable, but digitalis did not seem to help and there was not much change in her condition during the 2 months in hospital. The extreme congestion of the back and buttocks (when she lay in bed for some time) and of the dependent portions (in the ordinary position) suggested a danger of gangrene supervening once after a bruise, the area of the bruise necrosed without appreciable suppuration. Sir James Galloway afterwards told me that the patient died from gangrene of the skin about 1903 Necropsy showed no obvious visceral disease. The fat of the body was in excess. The heart and other viscera were small. The pituitary gland was probably not examined

The case reminds me of Turney s case of Cushing s pituitary syndrome, in which death ultimately took place from multiple ulcers and subcutaneous abscesses (*see* Weber 1926) In Turney s case there was an infection of the skin and subcutaneous tissue, but in some other cases of Cushing s syndrome there has been in the later stages a marked tendency to cutaneous necrobiotic changes and erythrocyanotic patches.

I need only mention the ischaemic necroses from arterial obstruction or prolonged pressure (bedsores) The little ischaemic ulcers on the feet in some cases of thromboangiitis obliterans, which are chronic, irritating, and often extremely painful, are sometimes incorrectly diagnosed. Nor need one here consider the infective gangrenes and spreading gangrenous ulcerations of the skin. The special tendency to gangrene in diabetes mellitus has been largely removed by modern insulin treatment. The cause of necrotic purpura—ecchymoses leading to gangrenous ulceration and sloughing—is not always clear

Chronic necrobiotic subcutaneous and cutaneous nodules of the rheumatoid arthritis type

Collins (1937) and others have conclusively shown that the characteristic nodules of rheumatoid arthritis consist of foci of fibrinoid degeneration and necrosis, surrounded by a border of tissue reaction notably with a palisade-like radiate arrangement of fibroblasts. (*Compare* Weber 1946d pp 31 and 48) Similar appearances have been described in necrobiosis lipoidica (*see further on*) and granuloma annulare (cf Ellis and Kirby-Smith 1942)—obviously conditions of totally different nature and different from each other From another direction compare the microscopical necrobiotic appearances in the nodes of some cases of periarteritis (polyarteritis) nodosa. Though the histological features of the nodules of rheumatoid arthritis are not absolutely pathognomonic of the disease, their presence does

help in the diagnosis of doubtful cases with quiescent joint-symptoms. Probably the temporary nodules, which disappear completely are of similar nature, the sero-cellular exudation being re-absorbed before any relatively large necrobiotic foci have formed. The nodules of acute rheumatism may well represent an analogous early stage of lesion without definite necrotic foci. Compare Aschoff's bodies in the heart in rheumatic fever and the minute focal necroses in the liver (and sometimes spleen and bone-marrow) in acute infectious diseases, especially enteric fever.

Atrophies and scleroses of the skin and subcutaneous tissues

Definition of terms

This is a very large subject, which cannot be dealt with in detail, comprising, as it does, the atrophodermias and sclerodermias, whether symmetrical and generalized or localized in stripes and patches (morphoea). The sclerodermic process is not rarely associated with an atrophic one. Sometimes apparently atrophic stripes and patches of subcutaneous tissue may so to speak, take the place of morphoeic scleroderma constituting a morphoeic atrophy of subcutaneous tissue

In regard to the use of the terms, scleroderma and sclerodermia, atrophoderma, and atrophodermia, I should like to make the following note. Strictly speaking scleroderma means hard skin and sclerodermia should mean a disease in which hard skin constitutes the prominent feature atrophoderma signifies atrophic skin and and atrophodermia should signify a disease in which atrophic skin is the main feature xeroderma is rough skin and xerodermia a disease in which rough skin is the main feature (e.g. a minor type of ichthyosis and xerodermia pigmentosa) leucoderma is white skin and leucodermia general condition in which white skin is a striking feature, notably vitiligo. But for convenience I have used the term morphoea (morphoeic or patchy sclerodermia) to include morphoeic (patchy) atrophy of subcutaneous tissue, in which there is no hardness and the cutis (derma) need not be involved at all.

Guttate cutaneous atrophy (guttate morphoea) must not be confused with the semi-fluid *grape-like protrusions*—apparently representing a regressive form of the molluscous fibromata of neurofibromatosis (Schweninger and Buzzi's grape-like mucoid type of molluscous fibromata) which can be pressed back through an aperture in the cutis into the subcutaneous tissue. Here one may also recall the small local patches of subcutaneous fat atrophy resulting (as an idiosyncratic reaction) from insulin infections. *More or less permanent* patches of atrophy of the panniculus adiposus may also result from relapsing febrile non-suppurative panniculitis (the Weber-Christian disease ') a rare inflammatory disease or syndrome of unknown origin.

Morphoeic atrophy of subcutaneous tissue

I have seen a few examples of the above mentioned morphoeic atrophy of subcutaneous tissue. I think it is a self-limiting *disease*, as is ordinary cutaneous linear morphoea (with or without involvement of the subcutaneous tissue). They both tend to commence in childhood or youth and ultimately to come spontaneously to a standstill. Morphoeic sclerodermia is sometimes associated with facial hemi-atrophy (Ehrmann and Brünauer 1931 Hunt, 1939)

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(3) An elephantiasis or scleroderma-like condition (see above on the sclerodermas) may supervene from lymphatic obstruction in various chronic lymphangitic infections besides filariasis, for instance chronic syphilitic, tuberculous, and septic conditions, but especially lymphogranuloma venereum. There are unexplained cases of chronic obstructive oedematous elephantiasis of the pudenda in both males and females.

(4) One should also mention allergic acute (and more rarely chronic) oedemas, including giant urticaria (when the subcutaneous tissue as well as the cutis is involved) and angioneurotic oedema of various parts. Probably Loeffler's temporary pulmonary oedema with blood-eosinophilia is usually nothing else than angioneurotic oedema in the lungs, of allergic nature, in subjects sensitized to ascariasis, which is very common in Switzerland. The phenomena of palindromic rheumatism and recurrent (including periodic) hydrarthrosis and of certain pararthritic (para-arthritic, para-articular) as well as periarthritic swellings are probably of allergic or allergic-like nature and intimately allied to angioneurotic oedema. They may be, perhaps, interpreted as manifestations of angioneurotic oedema of the synovial membrane of joints, tendon-sheaths and bursae and of adjoining fibrous and connective tissue. *See* Weber Palindromic Rheumatism (Weber 1946c), and The Question of Acute and Chronic Allergic and Allergic-like Conditions (Weber, 1946b).

Urticaria involving fasciae, tendon-sheaths, and periarticular structures, often without involvement of the skin, should not be forgotten. There may be severe pain or painful itching when the dense connective tissue of the tendon-sheaths of the fingers or of the palmar fascia is affected, and sometimes there may be slight accompanying ecchymosis. (Cf. Nixon (1916) on what he calls urticaria tuberosa of Willan) Frequent repetition probably sometimes leads to Dupuytren's contraction or the acquired form of Landouzy's camptodactylia In the causation of these conditions, slight repeated traumas doubtless play a part, probably by setting free a histamine-like substance, which, however, acts only in subjects predisposed by age or hypersensitization (Weber 1946c).

A similar explanation is, of course, plausible for the phenomena of urticaria factitia, notably that form which is illustrated in text-books as dermography or urticarial writing (on the back or other parts). This may be regarded as the expression of a constitutional peculiarity in subjects who often never suffer from ordinary attacks of urticaria, and is mostly not accompanied by much (if any) itching. It should be distinguished from the factitious urticaria which may be elicited during ordinary urticarial attacks, but not at other times. It is, in my opinion, no more a disease than is the constitutional peculiarity of greatly exaggerated knee-jerks in some individuals without organic nervous disease, strychnine poisoning or uraemia (Weber, 1906 and 1908a).

THE LIPOIDOSES

Thannhauser's monograph (1940) on this subject is the result of wonderful biochemical and clinical and literary study (Thannhauser 1940 Thannhauser and Magendantz, 1938). He presents a classification of cases that can be grasped even by those whose biochemical knowledge is deficient.

The most striking example of limited atrophy of the panniculus adiposus is furnished by the now well known disease termed lipodystrophia progressiva superior which though in depth it tends to involve the whole of the subcutaneous fat, is self limiting in extent, in some cases the face and neck remaining the only involved parts of the body

One must not forget to mention unilateral atrophies. Some cases of facial hemiatrophy appear to involve only the panniculus adiposus, as in lipodystrophia progressiva—in fact they may represent a unilateral type of lipodystrophia progressiva, limited to the head. In other cases, mostly in young individuals, all the soft parts and the cranial bones may be involved. Such cases are probably of organic nervous origin I think that they mostly commence in childhood or early adult life and are self limiting, as the process seems to come to a standstill. The cranial vault may present a depressed sagittal ridge, reminding one of the well-known unilateral stripes of morphoea on the forehead and scalp.

Here I would mention the trophic disturbances in extremities connected with syringomyelia and other developmental or acquired nervous lesions the Morvan type of syringomyelia is perhaps the best known example. It may apparently sometimes be the cause of ring-like constrictions of fingers or toes, as in ainhum, but occurring in persons who have never been in tropical or subtropical countries. Bony atrophy (terminal phalanges) may occur in Morvan-like cases, but likewise in some cases of the sclerodactylia type of scleroderma.

The glossy skin due to nerve injury or disease has been called atrophodermia neuritica

Senile atrophy of skin especially well marked on the backs of the hands, has been termed biotripsis the result of life-wear (Cheatle, 1909)

Atrophodermia vermiculata of the face occurs mostly in young subjects. Various names have been given to it, but its causation is not yet understood

The so-called *striae atrophicae* of the skin are probably all really varieties of the *striae cutis distensae* occurring in pregnant women—even the well-known striae patellares that have not rarely followed long confinement to bed for some infectious disease, especially enteric fever but some of the so-called idiopathic striae atrophicae in young persons are hard to explain (Weber 1935)

Infiltrations and accumulations

The oedemas

In this division the oedemas come first but I will instance only the less usual kinds.

(1) Nutritional oedemas, due especially to hypoproteinaemia and deficiency of protein in the diet.

(2) Congenital and developmental *(often familial) oedemas* of the Nonne-Milroy Meige type (Weber 1946d p 29) which are still sometimes confused with oedemas of renal or cardiovascular origin, especially if in older patients, they are associated with varicose veins. *Local recurrent erysipelas-like* attacks may complicate the clinical picture, and a kind of non tropical elephantiasis may ultimately supervene.

examination (Holmes, 1911). The child had been in a chronic apathetic state of decerebrate rigidity and died from pneumonia. Before Dr Holmes had finished his examination, a sister of the boy had died at another hospital of amaurotic family idiocy She (Fanny M.) was aged 1 year and 8 months at the time of her death, and an elaborate account of her case with post-mortem examination was published (Carlyll and Mott, 1911).

Both brother and sister undoubtedly died of amaurotic family idiocy (Tay-Sachs's disease), but I do not know of any case showing a kind of megalencephaly on necropsy from infiltration of the brain with lipoid cells. (Cf Hamburger's account (1927) of a case of Niemann-Pick disease combined with amaurotic idiocy in a girl aged 14 months.)

Dr D S. Russell has kindly allowed me to study her as yet unpublished paper on gargoylism ("Hurler's disease Pfaundler Hurler syndrome chondro-osteo-dystrophy of the Hurler type"), in which she includes her post-mortem findings. All the evidence suggests the presence of a grave disturbance of lipoid metabolism, and a relation to the Niemann-Pick disease, the Tay Sachs disease (amaurotic family idiocy) and Gaucher's disease (Russell, 1946).

The cholesteroloses or xanthomatoses

Classification into primary and secondary xanthomatoses

Primary xanthomatoses.—According to Thannhauser and Magendantz's (1938) scheme of classification, *primary or essential xanthomatosis* (*metaplastic reticular and histiocytic cholesterolosis*) is due to abnormal intracellular metabolism (? resulting from faulty enzymatic action) in the reticular and histiocytic elements of the reticular-endothelial system in the skin and/or other parts of the body Secondary or eruptive xanthomatosis can only be due to hyperlipaemia (hypercholesterolaemia) it occurs in individuals with essential xanthomatosis only when hyperlipaemia is present.

Cholesterol is present in every part of the body—whatever role it plays in the health of the individual—and the local disturbance of intracellular metabolism which leads to the local accumulation of cholesterol may occur at almost any part of the body This shows how many varieties in regard to the situation and distribution of xanthomatous lesions there must be. When one considers the various possible combinations of the lesions of primary xanthomatosis and the possibility of there being an eruptive (secondary) xanthomatosis superadded, the difficulties in classification become obvious.

Secondary xanthomatous eruptions.—These may be of two types (1) nodular the yellowish-brown nodules being usually surrounded by distended capillaries, giving them an appearance different from that of the nodules of essential xanthomatosis (2) papulo-vesicular The nodules of the second type are very itchy and may be mistaken for pustules. They become pigmented (maculo-papular). Secondary xanthomatous eruptions are due to the hyperlipaemia and not directly to the cause of the hyperlipaemia, as Major (1924) pointed out for the xanthoma of diabetes. The eruption depends upon the degree and duration of the hyperlipaemia. It rises and falls with it, and disappears when the hyperlipaemia is removed by diet, treatment of diabetes mellitus, etc. In essential xanthomatosis it occurs only when hyperlipaemia is present (*vide supra*).

Classification of the lipoidoses

The classification of the lipoidoses is by the particular lipoid of the disease. The essential lipoidoses are (1) essential (primary) xanthomatosis (2) Gaucher's disease and (3) the Niemann Pick disease According to Thannhauser's views they may respectively be termed (1) metaplastic reticular and histiocytic cholesterolosis (or cholesterosis as Thannhauser prefers) (2) metaplastic reticular and histiocytic cerebrosidosis and (3) metaplastic reticular and histiocytic sphingomyelinosis In the xanthomatoses ('cholesteroloses') the lipoid is cholesterol In the part of this article on the xanthomatoses I have, for convenience, sometimes spoken of hyperlipaemia, when the context makes it clear that it is the hypercholesterolaemic portion of the hyperlipaemia with which I am concerned

In *Gaucher's disease* the cerebroside *kerasin* is the lipoid which, by its accumulation in the large pale cells ('Gaucher cells') causes the enlargement of the spleen and, to a lesser degree, of the liver These cells accumulate also in the lymph-glands and bone marrow The accumulation of kerasin in the Gaucher cells is now thought to be due to a disturbance (by faulty enzyme action) of intracellular metabolism and not to an infiltration from the blood. The dermatological feature is a brownish discoloration of the skin in the older patients, especially that of the exposed parts (face and hands) The pigmentation is due to melanin There may also be a cuneiform (pinguecula like) thickening and pigmentation of the conjunctiva on both sides of the cornea in each eye. A familial tendency (Thannhauser says) has been noted in more than one-third of the number of reported cases, and there is a somewhat greater incidence among Jews. There is an acute infantile form of the disease which usually leads to death in the second year The adult form may first show itself in childhood or adolescence or sometimes not before adult life.

The *Niemann-Pick disease* is a rare, rapidly progressive, and fatal disease in infants, due to the accumulation of the diaminophosphatide, *sphingomyelin*, in the Niemann Pick cells as a result of faulty intracellular metabolism. These foamy Niemann Pick cells accumulate in most of the organs of the body There is a decided familial tendency and the affected infants are mostly Jewish. The disease is characterized by enlargement of the liver spleen, and lymph-glands. Diffuse pigmentation of the skin and patchy bluish black pigmentation of the oral mucosa constitute the dermatological features There are great points of resemblance between the Niemann Pick disease and the infantile form of Gaucher's disease, but histologically the resemblance to the Tay-Sachs disease (amaurotic family idiocy) is greater According to Scheidegger (1936) as quoted by Thannhauser (1940) the Niemann Pick and Tay Sachs diseases are histologically identical, although there are differences in regard to the areas of the brain involved In both diseases, by ophthalmoscopic examination during life, the cherry red spot of Gunn has been discovered Anyhow long ago in J M a Jewish boy (aged 2 years and 10 months at the time of death) under the care of my hospital colleague, Dr K. Fürth a condition of megalencephaly was present at the post-mortem examination

The brain weighed 1 450 grammes (exceeding the normal average weight of the adult male brain), and Dr Gordon Holmes kindly undertook the histological

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Cholesterol is present in every part of the body—whatever role it plays in the health of the individual—and the local disturbance of intracellular metabolism which leads to the local accumulation of cholesterol may occur at almost any part of the body This shows how many varieties in regard to the situation and distribution of xanthomatous lesions there must be. When one considers the various possible combinations of the lesions of primary xanthomatosis and the possibility of there being an eruptive (secondary) xanthomatosis superadded, the difficulties in classification become obvious.

Secondary xanthomatous eruptions.—These may be of two types (1) nodular the yellowish-brown nodules being usually surrounded by distended capillaries, giving them an appearance different from that of the nodules of essential xanthomatosis (2) papulo-vesicular The nodules of the second type are very itchy and may be mistaken for pustules. They become pigmented (maculo-papular). Secondary xanthomatous eruptions are due to the hyperlipaemia and not directly to the cause of the hyperlipaemia, as Major (1924) pointed out for the xanthoma of diabetes. The eruption depends upon the degree and duration of the hyperlipaemia. It rises and falls with it, and disappears when the hyperlipaemia is removed by diet, treatment of diabetes mellitus, etc. In essential xanthomatosis it occurs only when hyperlipaemia is present (vide supra)

A very remarkable case of secondary hyperlipaemia in a diabetic young woman has been recorded (Lawrence, 1946) in which at one time there was a secondary xanthomatous eruption of maculo-papular type She had also lipaemic hepato-splenomegaly and enlargement of the parotids and of all the lymphatic glands. There was also lipodystrophia, and the various features of the case have been made the subject of an elaborate study by Lawrence.

An unusual form of xanthoma eruptivum diabeticorum was described by Wise and Garb (1942) in a Negress, with keloid-like growths on the extensor surfaces and sides of the upper and lower limbs, having the features of both the nodular and the papulo-pustular types of secondary xanthoma complicating diabetes. For a review of 131 cases of eruptive xanthoma (diabeticorum) see Combes and Behrman (1941).

The hyperlipaemia which can give rise to eruptive (secondary) xanthomatosis may be

(1) the rare idiopathic (familial) hyperlipaemia with hepato-splenomegaly and secondary xanthomatosis in children (Holt and others, 1939 Buerger and Grütz, 1932 Goodman and others 1940)

(2) diabetic hyperlipaemia

(3) that due to chronic pancreatitis

(4) that occurring with the glycogen-storage disease of von Gierke

(5) that which may occur with lipoid nephrosis.

It may also be the hyperlipaemia associated with the first of the two groups of primary or essential xanthomatosis (*see further on*)

Classification of the primary or essential xanthomatoses

I shall not discuss further the secondary cutaneous xanthomatoses Thannhauser and Magendantz (1938) clinically distinguish two groups of primary xanthomatosis, though in all types of lesions the main histological findings are the same, namely xanthoma cells, granulomatous scar tissue with giant cells, and exudate cells, *varying according to the age of the lesion.* Absorption of cholesterol from xanthomatous lesions makes them become like granulomatous fibrous scar tissue.

(1) Their *first or hypercholesterolaemic group* comprises the following features (*a*) xanthelasma palpebrarum (*b*) plane and tuberous xanthomata (*c*) tendon and tendon-sheath xanthomata (*d*) xanthomatous involvement of the wall of the bile-ducts with xanthomatous biliary cirrhosis (*e*) xanthomatosis of the wall of the blood vessels and endocardium (*f*) high values of total cholesterol in the blood serum, increased fraction of lecithin and cephalin and increased fat (*g*) eruptive (secondary) form of skin xanthomata (consequent on hypercholesterolaemia) (*h*) xanthoma cell nests in the spleen, lymph nodes, and liver

(2) The features of their *second or normocholesterolaemic group* are (*a*) xanthomata disseminata of the skin (in axillae, flexor surfaces of elbows and knees, etc.), mouth and larynx (*b*) xanthomatous involvement of the pituitary gland and tuber cinereum with diabetes insipidus (*c*) xanthomata in the brain and medulla (*d*) xanthomatous nodules on the dura mater and orbit (*e*) osseous xanthomata (*f*) xanthomatous involvement of the lung and pleura with consequent fibrosis (*g*) normal or high normal total cholesterol in the blood-serum, normal lecithin

and cephalin fraction, and normal fat (neutral fat) (*b*) scattered nests of xanthoma cells in the spleen, lymph nodes, and liver (also present in the first group).

Writing on hereditary xanthomatosis, Bloom, Kaufman, and Stevens (1942) state that, in agreement with the above classification—accepted by Thannhauser and Magendantz, and confirmed by Montgomery (1939 1940) and other investigators—primary essential xanthomatosis may be divided into two main groups (1) xanthoma tuberosum, etc., the hypercholesterolaemic group and (2) xanthoma disseminatum, etc., the normocholesterolaemic group. *Xanthoma disseminatum* consists of numerous fine papules and plaques on the flexor surfaces of the extremities, especially in the axillary folds. The mucous membranes of the mouth, pharynx, and larynx are often affected and, as a result of involvement of the pituitary gland, there is frequent occurrence of diabetes insipidus. With this group Thannhauser and Magendantz also associated involvement of the bones, lungs and brain and the Hand Schüller-Christian syndrome. *Xanthoma tuberosum*, on the other hand, is characterized by nodules, tumours, and plaques, located predominantly on the elbows, knees, and buttocks and over the Achilles tendons, and the tendons and joints of the fingers, toes, hands, and feet. In the xanthoma tuberosum group there is frequent association with *cardiovascular disease* and hereditary incidence is especially to be noted, whereas apparently in only one case of xanthoma disseminatum has familial occurrence been detected (Mackenzie, 1882).

Association with hypercholesterolaemia

In my little book, *Cutaneous Xanthoma and Xanthomatosis of Other Parts of the Body* (Weber 1924), although I referred to a number of typical cases of xanthomatous biliary cirrhosis' such as Thannhauser and Magendantz (1938) connect with their first (hypercholesterolaemic) group of essential xanthomatosis, I thought that the symptoms (including the cutaneous xanthomatosis) were secondary to chronic biliary obstruction, and did not recognize that the xanthomatosis of the biliary passages and liver (connected with their first group of essential xanthomatosis) led to the chronic jaundice and (xanthomatous) enlarged and cirrhotic liver Due credit is given by Thannhauser and Magendantz to the first account by Addison and Gull (1851) and to the writings of other English physicians of that time.

When there is much destruction of liver parenchyma, the ratio of free cholesterol to cholesterol esters in the blood-serum becomes changed, the cholesterol esters being relatively less. An inverse ratio suggests involvement of the liver even when clinical signs are absent. Thannhauser and Schaber (1923) already showed that cholesterol esters were relatively decreased in cases of parenchymatous liver disease. The symptom-triad in xanthomatous biliary cirrhosis, as stressed by Thannhauser and Magendantz (1938), consists in (1) enlarged liver and spleen with jaundice of years duration (2) tuberous and plane xanthomata of elbows knees, etc. (3) hypercholesterolaemia with inverse ratio of cholesterol to cholesterol esters. The jaundice may sometimes be intermittent.

Personally I believe that everyone (in his own interest as well as the interests of his employers and dependants) in whom, or in his relatives, there are any signs or symptoms suggestive of Thannhauser and Magendantz's first (hypercholesterolaemic) group of primary essential xanthomatosis, should be repeatedly

examined for hypercholesterolaemia This should be done when he is on an ordinary mixed diet, but perhaps also with the help of test-diets specially rich in animal fats Care should be taken that at the time of the test the patient has not, for some reason or other been having a diet very poor in animal fats, which is likely temporarily to lower his blood-cholesterol. Those tested should include *all individuals* showing xanthelasma palpebrarum (however slight—even pigmented dark circles round the eyes without obvious xanthelasma) or tuberous or plane xanthoma of any kind those with chronic biliary or hepatic symptoms with or without evidence of gall stones, and those with symptoms suggestive of coronary sclerosis In many such cases the timely avoidance as far as possible of cholesterol and excess of animal fats in the diet would *I think* conduce greatly to health and longevity by preventing or hindering hypercholesterolaemic troubles and the premature onset of symptoms connected with aortic atheroma and coronary sclerosis. *In fact, I am inclined to think that if hypercholesterolaemia were detected in children* or in relatively young adults—with or without obvious xanthoma, but especially with a hypercholesterolaemic family history—the use of a fat poor (poor in animal fat) diet might be beneficial by hindering the development, not only of obvious xanthomatosis, but also of grave atheroma of aorta and coronary arteries.

A striking case illustrating connexion of tendon xanthomata with cardiovascular disease was shown by Anderson (1943)

> The patient, a woman aged 60 years, had xanthomata of tendons and tendon sheaths, with juxta-articular subcutaneous nodules, but no cutaneous xanthomata blood-serum cholesterol 400 mg. per cent symptoms of angina pectoris on effort since the age of 52. A sister of the patient was known to have had similar nodules and angina of effort (For an excellent paper on xanthoma of tendon-sheaths and synovial membranes, see Galloway Broders, and Ghormley 1940)

One may remember that there seems to be a certain relation between gall-stones, especially solitary stones of the gall-bladder and atheroma (Gross, 1929).

I cannot easily forget the fine-looking London surgeon whose case I mentioned in my little book, *Cutaneous Xanthoma and Xanthomatosis of the Other Parts of the Body* (Weber 1924 p 14)

> In 1902, at the age of 41 years, he had tuberous xanthomatosis of the elbows. About 7 years later he commenced to suffer from intermittent claudication of both lower extremities, at first slight but gradually increasing in severity This intermittent claudication continued till his death in 1913 and post mortem examination proved that it was due to severe atheroma of the abdominal aorta and iliac arteries.

Various aetiological factors

Routine examinations would sometimes bring to light other metabolic disturbances (and various diseases) previously unsuspected such as commencing diabetes mellitus with high blood-sugar

With regard to possible precipitating factors in xanthomatosis, the influence of slight repeated traumata *is evidenced by the preference of xanthomata for the elbows* and parts of the skin subject to frequent friction such as the buttocks. Dr Alice Carleton, at the British Association of Dermatology (6th July 1945), showed a case of multiple tuberous xanthoma *following* gold injections.

Practical considerations

From a practical point of view in every xanthomatous condition the patient should be examined for hyperlipaemia, diabetes mellitus, and jaundice. Diabetes insipidus may of course, be a main feature in certain cases, namely in the Hand-Schüller-Christian syndrome and whenever xanthomatous lesions in the pituitary gland and its neighbourhood occur in the xanthomata disseminata group.

In regard to the effects of diet on hyperlipaemia and xanthomatosis and arterial atheromatosis, one must remember that, although it may doubtless make a difference in some cases, human beings differ from the experimental rabbits, which develop aortic atheroma and xanthomatous storage from excess of animal fat in the diet much more readily In some human families there is certainly a tendency to aortic atheroma, which may probably be increased by faulty diet. Just as in allergic diseases it is only in allergic individuals that hay fever asthma, urticaria, etc. can be excited by certain allergens, so, probably it is only in predisposed individuals that moderate fatty excess in diet can favour xanthomatosis and atheromatosis.

The whole question of the relation of cutaneous xanthomatosis to ordinary cardiac and aortic atheroma remains unsettled, but that in some families there is a special incidence of palpebral xanthelasma, as well as a special tendency towards atheroma of the heart and large arteries, there can be little doubt (cf., however Aschoff, 1932).

In most young persons with mild xanthelasma palpebrarum the xanthomatous process remains stationary (I think) if they live normally even without special anti-hyperlipaemic diet. The xanthelasma palpebrarum is probably related to fuller forms of xanthomatosis in a somewhat analogous way to the relation of ordinary *café-au-lait* pigment-patches to fully developed neurofibromatosis of von Recklinghausen.

The early onset of arcus senilis or arcus lipoides corneae (gerontoxon) has apparently little prognostic value regarding longevity I do not know whether the same supposition should be accepted for arcus lipoides myringis apparently an analogous condition of the ear-drum (Berberich, 1939) and I think it should not be accepted in regard to cholesterol disturbances of the interior of the eye, including synchysis scintillans —a wonderful sight by ophthalmoscopic examination.

Thannhauser and Magendantz (1938) find that cases of primary or essential xanthomatosis of their first (hypercholesterolaemic) class show a marked decrease of blood-cholesterol, as well as of the other blood-lipoids, after a period of cholesterol-poor and fat-poor diet, such as has been described by Thannhauser (1936) Such diets contain only vegetable fats, because plant-sterols are not absorbed (Schönheimer 1933). Diet, they find, has no effect in their second (normocholesterolaemic) class, but in both classes they tried in addition small doses of thyroidin, 1 gram daily with good effect in the first class and no obvious result in the second class. X-ray therapy (Sosman, 1932) gave satisfactory results in the bone and dura mater lesions of the second class. It is naturally in cases of secondary xanthomatous eruptions from hypercholesterolaemia that dietetic treatment has its most striking effects, in conjunction with treatment of diabetes mellitus (if present) or of pancreatic or nephrotic disease.

Thannhauser and Magendantz (1938 p 1725) as should be noted, mention 3 cases in which features of both groups of essential xanthomatosis were combined. Apart from this, it is obvious that there may be many clinical combinations in each group. I thought at first that a case of diabetes insipidus, due to xanthomatosis of the pituitary gland without xanthomatosis elsewhere, had escaped their classification, but of course it finds a place in their second group (Weber and Schmidt, 1916. Weber 1924 p 21)

In conjunction with Schmidt (Weber and Schmidt, 1916) I described a case of diabetes insipidus in a man (F A——), aged 37 years, who died from pulmonary and laryngeal tuberculosis on 21st June, 1915. In August 1913—that is to say about 2 years before his death—he had suddenly commenced to suffer from diabetes insipidus, which persisted until his death. In the hospital, his urine, which was of about the same specific gravity (1 000) as ordinary pure water and was pale, clear and free from albumin and sugar averaged about 10 litres in the 24 hours—sometimes more, sometimes less. on one day he passed as much as 13,250 c.c. His blood-serum gave a negative Wassermann reaction. At the post mortem examination, besides the above-mentioned severe pulmonary and laryngeal tuberculosis, a peculiar change was found in connexion with the pituitary gland, which (at that time) I thought was quite unique.

The pituitary fossa was not much enlarged, but the posterior lobe of the pituitary gland (pars nervosa) was obviously relatively greatly enlarged and abnormal. It enclosed almost completely the anterior lobe (pars glandularis), and was of a yellowish-brown colour. This xanthic colour likewise infiltrated the posterior wall of the pituitary fossa, i.e. the dorsum sellae turcicae. The relatively large size of the posterior lobe was accounted for by its containing clusters of foamy lipoid-containing cells, a pigment of the nature of lipochrome being doubtless the cause of the yellowish-brown coloration which I have mentioned. The cells in question were rather large, and their pyknotic small nuclei stained deeply with haematoxylin. Their over-abundant cytoplasm, which in ordinary paraffin sections appeared finely vacuolated or foamy was shown by appropriate staining in frozen sections to contain innumerable granules or minute droplets of a fatty or lipoid substance. I have no doubt that the cells in question were of the nature of xanthoma cells, but no xanthomatous changes were discovered in any other part of the body

The main landmarks in the discovery of the Hand-Schüller-Christian syndrome are too well known to need any repetition here. The important writings of Rowland (1928 1929 1932) helped greatly in the development of our knowledge of xanthomatosis and lipoid granulomatosis or reticulosis (Chester 1930) or cholesterol granulomatosis (Horsfall and Smith, 1935) of cranial and other bones in the second (normocholesterolaemic) group of essential xanthomatosis. Other papers on the same subject have been those of Höfer (1930) Rietschel (1932), Snapper and Parisel (1933) Morison (1934) Horsfall and Smith (1935), Shelling and Voshall (1935) Fraser (1935), Teschendorf (1936), Atkinson (1937), Hankey (1938) Hancock (1939) Hilton and Eden (1941) Currens and Popp (1943—a case with pulmonary fibrosis) Matthews (1946)

Dyke's paper (1928) on hypercholesterolaemic splenomegaly helped to explain the jaundice and progressive enlargement of the liver and spleen in some cases of the first (hypercholesterolaemic) group. One of the latest contributions to the subject of xanthomatous biliary cirrhosis is that of Hoffbauer and others (1945).

Their patient, in whom there were tendon xanthomata, had an enlarged liver which, clinically was thought to be due to xanthomatous biliary cirrhosis, but post-mortem examination showed only extensive diffuse portal cirrhosis of the Laennec type. For the classical works of L. Pick and of L. Pick and F Pinkus, as well as numbers of other great contributions, I must refer readers to the bibliography given by Thannhauser (1940).

Illustrations of primary or essential xanthomatoses

A remarkable example of Thannhauser's second group, in a 9-months-old infant, was demonstrated by Dr D. S. Russell at the Pathological Section of the Royal Society of Medicine on 20th February 1945 (not yet published) The case was one of lipoid granulomatosis (lipoid reticulosis) involving the cranium and vertebral column (the collapse of one vertebra had left only a wedge-shaped remainder), the thymus (converted into a large tumour like mass) the lungs and some other parts. The spleen was not involved. The pituitary region was not specially affected, and there was no diabetes insipidus as in typical cases of the Hand Schüller-Christian syndome (Russell, 1946).

An excellent example of Thannhauser's first (hypercholesterolaemic) group with permanent jaundice and greatly enlarged liver evidently xanthomatous biliary cirrhosis, which occurs mostly in females, was shown by Dr C. P Petch (for Professor de Wesselow) at the Clinical Section of the Royal Society of Medicine on 8th November 1946. The patient, a woman aged 55 had xanthelasma palpebrarum, tuberous xanthomata at elbows and knees, and xanthoma planum of palmar creases Total blood-serum cholesterol 639 milligrams per cent (free cholesterol 311 ester cholesterol 328). Blood-sugar (fasting) 95 milligrams per cent. Positive direct van den Bergh reaction. (*See* Petch, 1946.)

A somewhat similar case in a woman, aged 31 was shown by Dore and de Wesselow (1926), with jaundice of 2 years duration but no gall-stones on exploratory operation. Blood-serum cholesterol 1,325 milligrams per cent. Xanthoma of laparotomy scar

Thannhauser's second (normocholesterolaemic) group of essential xanthomatosis, with what he calls xanthomata disseminata of the skin, is well illustrated, I think, by an infant, aged 2 years, shown by *Tate* (1933) and one shown by Dowling (1934) the former had intermittent diabetes insipidus, though skiagrams of the skull and long bones appeared normal. This xanthomata disseminata group is specially well illustrated by Logan *Turner's case*, a young woman with extensive distribution of the xanthomata in the mucosa of the respiratory tract (Turner 1925 Turner *et al.*, 1925).

Low's account (1910) of xanthoma tuberosum multiplex with lesions in the heart and tendon-sheaths illustrates a type of Thannhauser's first (hypercholesterolaemic) group of essential xanthomatosis.

Other and uncertain forms of cholesterolosis or xanthomatosis

Xanthomatous or lipoid rheumatism

In a man, aged 35, with symptoms resembling severe rheumatoid arthritis, para-articular thickenings and subcutaneous and cutaneous nodules developed,

which, on microscopic examination were found to differ from those of the Collins rheumatoid arthritis type (Weber and Freudenthal 1937 Weber 1946d, p. 39).

> Biopsy of the nodules showed large masses of cells constituting the main feature. These cells were scattered irregularly between the bundles of collagen tissue in all parts of the cutis. The cells were so numerous that their mass exceeded that of the collagen tissue, the bundles of which were pressed aside rather than destroyed. The cells were conspicuous by their size, which was up to four times that of an epithelial cell Most of them were multinucleated and had 3–5 or more bright nuclei (with definite nucleoli), frequently aggregated. They had a well-stained, well-defined, abundant, round, oval, or polygonal cytoplasm. The cytoplasm was homogeneous and even by oil-immersion did not show a foamy structure. In some areas, however the cytoplasm was stained a faint red by Sudan III No double refraction.

Freudenthal suggested that such giant-cells (which were not like the giant cells described by Touton (1885) in xanthoma) might possibly represent a kind of pre-xanthoma cells There was no proof however that these cells would actually become xanthoma cells, though they might resemble an intermediate stage in development towards typical foam-cells (Arzt, 1919) Microscopically as Freudenthal admitted, they showed a marked resemblance to Gaucher cells

> The patient slowly improved under various treatments, especially at the Middlesex Hospital (teeth removed, fat-poor diet, orange juice with glucose, massage, and injections of some kind—records lost owing to the recent war), and when I saw him in November 1943 he could walk about well and do night-watching, though he could not flex his right hip normally He still had knotty rheumatoid hands, with nodules at the knuckles and over the elbows. There was also a good deal of crackling when he flexed and extended his knee-joints I found him still better in 1947

In this case the presence of cholesterol in the lesions was never absolutely proved. The blood-cholesterol on one occasion was 350 milligrams per 100 cubic centimetres, but fell to 110 milligrams per 100 cubic centimetres. I can find no literature on the subject, excepting perhaps Layani s case of xanthomatous chronic deforming rheumatism (Layani 1939 Layani and others 1939) which was that of a woman, aged 46 years, who had a deforming rheumatoid disease of 15 years duration. In addition to the xanthomatous condition she had prolonged jaundice with hepatomegaly (doubtless xanthomatous biliary cirrhosis) and there were other remarkable features in the account. By the kindness of Dr George Graham and Dr E. T D Fletcher however I have been able to examine two other men in England possibly suffering from a somewhat similar syndrome. In both my patient and Dr Graham s patient a florid increase of the subcutaneous infiltrations developed after they had been lying on their backs in bed for days The infiltrations then tended to become actually confluent in parts over their shoulders and backs, specially heated from lying on their backs in bed Another remarkable feature in both Dr Graham s patient and mine was the occurrence (in addition to the large and medium sized nodules) of minute (miliary) superficial nodules ('droplets') evidently arising in the outer part of the cutis these appeared for a time in great numbers on the nose, forehead and other parts of the face, and then disappeared without leaving a trace they may have represented a secondary xanthomatous eruption but we had no proof of accompanying hyperlipaemia. The ultimate atrophy or involution of large nodular infiltrations in my case was remarkable

For subsequent history and examinations in Dr Graham's and Dr Fletcher's cases, *see* references Graham and Stansfeld, 1946, and Fletcher 1946.

Lipoid-proteinosis (*Urbach and Wiethe* 1929)

This has been claimed to be a lipoid-protein (phosphatide soluble in acetone) infiltration of the skin and mucous membranes of the mouth, pharynx, and larynx, leading to warty scar-like lesions of the face and hard yellowish lesions in the mucous membranes. When the larynx is affected, the disease may lead to stenosis and necessitate tracheotomy and the permanent use of a tracheal cannula. (*See Urbach, 1929* Urbach and Wiethe, 1929 Tripp, 1936.) Thannhauser and Magendantz (1938, p. 1709) attach lipoid-proteinosis to their xanthomata disseminata group of essential xanthomatoses.

Necrobiosis lipoidica diabeticorum (*Oppenheim*, 1929 *Urbach*, 1932)

This is characterized by the appearance of firm violet brown plaques with yellowish centres on the extremities. Histological examination (biopsy) shows a necrobiotic change with diffuse brownish coloration on Sudan staining. Most of the patients have diabetes mellitus or at least hyperglycaemia, and are improved by insulin treatment and by a fat-poor and carbohydrate-rich diet against hyperlipaemia. As to the microscopic features and their interpretation see Nicholas (1943) and Ellis and Kirby Smith with a discussion (1942). In regard to cases in England, see especially Klaber (1934).

Cerebral form of generalized cholesterolosis (*van Bogaert, Scherer and Epstein*, 1937)

Perhaps this cannot be made to fit into the second (normocholesterolaemic) group of primary or essential xanthomatoses, according to the classification of Thannhauser and Magendantz (1938). Thannhauser (1940) points out that in van Bogaert's case the localization of the nervous lesions is altogether different from that in other cases.

Xanthomatous formations in inflammatory tissue and true tumours

(1) Formation of xanthoma cells in traumatic and inflammatory conditions of the breast and in chronic inflammatory and ischaemic necroses and scleroses in fatty tissue and lipomata (2) xanthomatous lipomata (3) neurofibromata with xanthoma cells (4) xanthomatous transformation of the mesentery and intestinal lipodystrophy of Whipple (1907) (5) inflammatory conditions of various organs, e.g. so-called strawberry gall-bladder xanthomatous salpingitis xanthomatous pyelonephritis (Österlind, 1944) secondary xanthoma with lupus erythematosus (Netherton, 1945) (6) xanthoma in lineae albicantes of elderly women (Weber 1908b) and in scars, with or without hyperlipaemia (7) cholesterol pericardial and pleural effusions (Moll and Fowweather 1940) (8) cholesteatomata of the choroid plexus, aural cholesteatomata (9) xantho-naevo-endotheliomata (McDonagh, 1912) (10) congenital epulis of the xanthoma type (11) xanthomatous polycystic lymphangiomata (12) single xanthomatous giant-cell tumours of bones and joints (so-called xanthomyelosarcomata and osteoclastomata) (de Santo and Wilson, 1939 Galloway *et al.*, 1940) (13) the well-known malignant Grawitz tumours of the kidney still wrongly termed hypernephromata by many surgeons (14) epithelial tumours with giant cells.

which on microscopic examination were found to differ from those of the Collins rheumatoid arthritis type (Weber and Freudenthal 1937 Weber 1946d, p. 39).

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Perhaps this cannot be made to fit into the second (normocholesterolaemic) group of primary or essential xanthomatoses, according to the classification of Thannhauser and Magendantz (1938). Thannhauser (1940) points out that in van Bogaert's case the localization of the nervous lesions is altogether different from that in other cases.

Xanthomatous formations in inflammatory tissue and true tumours

(1) Formation of xanthoma cells in traumatic and inflammatory conditions of the breast and in chronic inflammatory and ischaemic necroses and scleroses in fatty tissue and lipomata (2) xanthomatous lipomata (3) neurofibromata with xanthoma cells (4) xanthomatous transformation of the mesentery and intestinal lipodystrophy of Whipple (1907) (5) inflammatory conditions of various organs, e.g. so-called strawberry gall-bladder xanthomatous salpingitis xanthomatous pyelonephritis (Österlind 1944), secondary xanthoma with lupus erythematosus (Netherton, 1945) (6) xanthoma in lineae albicantes of elderly women (Weber 1908b) and in scars, with or without hyperlipaemia (7) cholesterol pericardial and pleural effusions (Moll and Fowweather 1940) (8) cholesteatomata of the choroid plexus, aural cholesteatomata (9) xantho-naevo-endotheliomata (McDonagh, 1912) (10) congenital epulis of the xanthoma type (11) xanthomatous polycystic lymphangiomata (12) single xanthomatous giant-cell tumours of bones and joints (so-called xanthomyelosarcomata and osteoclastomata ") (de Santo and Wilson, 1939 Galloway *et al.*, 1940) (13) the well-known malignant Grawitz tumours of the kidney still wrongly termed hypernephromata by many surgeons (14) epithelial tumours with giant cells.

Cholesterol may be deposited in necrotic tissue in various parts of the body as in cholesterol tumour from craniopharyngioma of the pituitary body (Weber, Worster Drought, and Dickson 1934) various necrotic tumours, old empyemas, and collections of inspissated pus.

THE AMYLOIDOSES

Apart from the generalized cases of *secondary* amyloidosis, due to prolonged suppuration to tuberculous caries and to other less well recognized causes, such as syphilis and Hodgkin s disease, in which the amyloidosis has notable predilection for the liver spleen, kidneys, and intestinal mucosa, many cases of atypical *primary* amyloidosis have from time to time been described in which none of the recognized causes of secondary amyloidosis are present and in which the liver and other favourite sites of the secondary disease are not—or are only relatively little—affected.

In at least some of these primary cases the staining reactions have likewise been atypical, the characteristic metachromatic staining being faint, or obtained with relative difficulty and not by all of the recognized methods, thus giving rise to the suspicion that the abnormal material present is not wholly amyloid, but consists, at least in part, of some chemically allied substance or substances. In fact, an amyloid group of substances has been surmised (Schmiedeberg, 1920 Rosenheim and Wright, 1933 Weber Stott Cade, and Pulvertaft, 1937).

Primary systematized amyloidosis

These cases are apparently due to an unknown disturbance of the protein metabolism and in some of them (Lubarsch Pick syndrome) a striking clinical feature has been a diffuse, more or less symmetrical enlargement of the tongue, amyloid macroglossia, sometimes combined with pseudo-myotonic stiffness of involved skeletal muscles with a kind of intermittent claudication (due doubtless to arterial involvement) and with pseudo-sclerodermic hardness of involved areas of skin. (For most of the literature see Weber *et al* 1937 Barnard *et al* 1938 Dillon and Evans, 1942.) Since 1937 I have myself been shown two further (as yet unpublished) examples of the Lubarsch Pick type of primary generalized amyloidosis in men

In some primary generalized cases the nerves may be specially involved (de Navasquez and Treble, 1938) or the lymph nodes (Morgan, 1946)

The relatively not very rare association of multiple myeloma (myelomatosis) with amyloidosis has given rise to the suggestion that in such cases both the amyloid substance and the Bence-Jones protein in the urine may be produced by the break *down of myelomas of the plasma-cell type* (Stewart and Weber 1938 Magnus-Levy 1933 1936, 1938)

Primary local amyloidoses

There is a considerable scattered literature on local so-called *amyloid tumours* in the tongue, nose, conjunctivae, or upper respiratory passages or lungs sometimes the heart is specially selected sometimes the seminal vesicles, ureters or urinary bladder *Amyloid tumours or circumscribed or diffuse amyloid changes*

confined to the skin, have often been described (see references given by Weber *et al.*, 1937). Such changes may well be due to a disturbance of *local intracellular metabolism.*

THE CALCINOSES

Calcinosis is a convenient term for a condition in which calcareous deposits in various parts of the body occur It may be primary or secondary

Secondary calcinosis is due to high blood-calcium (1) caused by hyperparathyroidism—from parathyroid adenoma or connected with severe chronic renal disease (Wigley and Hunter 1945) (2) from excessive destruction of osseous tissue, as by neoplasms (Virchow's metastatic calcareous deposits) (3) from excessive



FIG. 29 —A. M. H. Gray's case of lichen amyloidosis. (*By courtesy of Messrs. J. & A. Churchill.*)

intake of vitamin D—experimentally in small *animals* and rarely in human infants. In a young adult treated in France with vitamin D for lupus vulgaris, some calcification is reported to have occurred about the finger-joints.

Primary calcinosis— calcinosis universalis or calcinosis interstitialis universalis —is a rare disorder of the calcium-phosphorus metabolism in children and young persons, for which no certain treatment is known other parts besides the skin and subcutaneous tissue are involved (cf Skossogorenko, 1932 Salvesen and Böe, 1937). Calcinosis universalis may accompany dermatomyositis in children (Hecht, 1940).

For a review of the literature of calcinosis, see Atkinson and Weber (1938) and Weber (1946d, p. 73). In very rare cases of calcinosis a remarkable feature must be mentioned, namely the formation in the subcutaneous tissue over certain areas of a kind of lymph sacs reservoirs or cushions which fluctuate like

water beds when pressed on This condition of lymph sacs may perhaps also occur without calcinosis. (*See* Sheldon, 1934 Kunitzky and Melchior 1916.)

The not very rare local calcification in fingers of patients with sclerodactylia (Scholefield and Weber 1911) and Raynaud's syndrome ought perhaps to be called secondary—an example of secondary accumulation of calcium salts in damaged or necrobiotic tissue.

Calcium salts may be deposited in degenerating and necrotic material in various parts of the body including caseous tuberculous lesions, degenerating neoplasms, atheromatous arteries, retained sebaceous accumulations (as old sebaceous cysts)



FIG. 30.—W Freudenthal and S. R. Brünauer's case of myxoedema papulosum et annulare. (*By courtesy of the Royal Society of Medicine.*)

and so-called scrotal calcinosis (Weber 1936) inspissated pus, and old haematomata.

THE MUCINOSES

Myxoedema due to hypothyroidism manifests itself mainly as a mucinous infiltration of the cutis and subcutaneous tissue but besides the generalized condition there are sometimes diffuse myxoedematous areas and circumscribed papular tuberous, nodular annular lichenoid or moniliform myxoedematous lesions (Freudenthal and Brünauer 1942) (Fig. 30) The terms myxoedema moniliforme (Freudenthal, 1932) (Fig. 31) lichen ruber moniliformis and morbus moniliformis lichenoides are practically synonymous (Mumford and Barber 1943)

Remarkable swellings on the legs—often sharply circumscribed hard pretibial plaques—sometimes occur in patients with hyperthyroidism not rarely after the

removal of a thyrotoxic goitre. They have been called variously circumscribed myxoedema localized pretibial myxoedema in association with toxic goitre elephantiastic papulonodular myxoedema myxoedema circumscriptum thyrotoxicum myxoedema (gravitational) of legs etc. (Pillsbury and Stokes, 1931 Ingram, 1933 Dowling, 1934 1935 Trotter and Eden, 1942 Sunseri, 1943 Cohen, 1946 Forman, 1946).

THE ELASTOSES AND COLLOID CHANGES

Elastosis dysplastica or elastosis dystrophica (Böck, 1938) is the best name for the developmental dysplastic disease usually termed pseudo-xanthoma elasticum (Fig. 32). The term elastosis atrophicans was suggested by Lewis and Clayton (1933), who found that in 16 cases reported in the literature the patients likewise manifested angioid streaks in the retina. These streaks are now

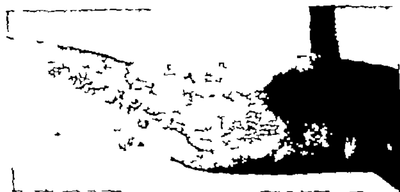


FIG. 31.—P. B. Mumford and H. W. Barber's case of myxoedema moniliforme (Freudenthal), described in *Proc. Roy. Soc. Med.*, 1943, 36, 286. (*From a photograph kindly lent by Dr H. W. Barber.*)

recognized as part of a syndrome—which may best be termed *elastosis dysplastica*—due to a general dysplastic condition of the elastic tissue. Other symptoms are due to degenerative (dystrophic or dysplastic) changes of the elastic fibres in the walls of arteries. Areas of cutis laxa may be present in some cases (cf. Freudenthal, 1932 Heggs and Williamson-Noble, 1936 Wright and Freudenthal, 1943). This cutis laxa should be distinguished from the cutis laxa of the Ehlers-Danlos syndrome, in which it tends to be specially marked about the elbows and knees, and from the molluscous folds and flounces of neuro-fibromatosis, and also from certain rare developmental cases in which the skin seems to be hyperelastic and loosely attached to the deeper parts.

Epidermolysis bullosa has been thought to be connected with an inborn hereditary deficiency of elastic fibres of the skin.

The common *cutis rhomboidalis nuchae* is said to be due to a lipoid degeneration of the elastic fibres in the affected skin of the neck. It has been termed imbibitio

lipoidica telae elasticae degeneratae (Urbach, 1934) (Cf also Percival (1947), on *senile elastosis*)

Colloid degeneration of the skin (the so-called colloid milium of the face and elsewhere) is due to colloid degeneration mainly of the collagen and elastic fibres of the connective tissue of the corium, especially about the glands. It is not really a milium disorder at all whereas so-called *colloid acne* is apparently really due to a degeneration of acne lesions.

Berlin (1946) proposes the name, *degeneratio colloidalis cutis solaris* to differentiate the condition from similar cutaneous degeneration in the aged and to stress the aetiological importance of the sun s rays. The parts of the skin exposed to sunlight are specially affected Very significant (he says) is the common associa-



FIG. 52.—J E. M Wigley and W Freudenthal s case of pseudo-xanthoma elasticum with dermatolysis of Alibert, illustrating loose folds over skin of abdomen. (*By courtesy of the Royal Society of Medicine*)

tion with other manifestations, generally recognized as sun effects, such as pigmentations, telangiectasia, exaggeration of the normal furrows and the formation of pathological ones. The above mentioned cutis rhomboidalis nuchae also shows colloid degeneration, and Berlin points out that Jager s patient (according to his illustration) in addition to the colloid nodules, had typical cutis rhomboidalis nuchae. The involvement of cutaneous blood vessels (telangiectatic changes may be present) in the colloidal degeneration gives rise to purpuric lesions— purpura solaris —and proneness to a kind of purpura factitia from the nail-pressure test. Berlin also describes an abortive form of colloid degeneration of the skin, which may escape attention until revealed by local purpura and the nail pressure test.

Juvenile elastoma, as described by Weidman and others (1933) is, it seems, a rare congenital hamartomatous defect of the skin, characterized histologically by swollen bundles of elastic tissue.

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CHAPTER 15

THE PREVENTION OF CUTANEOUS DISEASES EXCLUDING INDUSTRIAL MALADIES

F. A. E. Crew

INTRODUCTORY APOLOGIA

That which follows is an attempt to provide a contribution which seems to be lacking from most, if not all, of the existing text books on dermatology. It is offered by one who though confessedly ignorant of the technicalities of the subject, is of necessity interested in the preventive and social aspects of cutaneous diseases.

Reliable and comprehensive information concerning the extent of morbidity due to diseases of the skin in the general population is not available. For example, figures such as those of the Registrar-General for Scotland in his Report for the year 1944 which show that diseases of the skin and cellular tissue were responsible for 187 out of a total of 64,603 deaths, provide no measure whatsoever of the total sickness due to cutaneous disease. Morbidity figures for the Army (at home) during the war years, however suggest that possibly not less than 3-4 per cent of the total major morbidity requiring admission to hospital and rendering the individual incapable of leading a normal life may in the general population, also be due to diseases of the skin, and that of those complaints which together are responsible for some two-thirds of minor morbidity calling for medical attention and yielding discomfort and temporary inefficiency—skin diseases, tonsillitis, gastro-intestinal troubles and the common cold —the first probably exceeds all the rest in respect of incidence and social importance. Cutaneous diseases must loom largely therefore, in considerations concerning preventive and social medicine.

The fact that in no text-book on dermatology or hygiene, available for consultation, is there any adequate attempt to proffer guidance on this aspect of the subject cannot be without significance. It is clear that the knowledgeable and experienced deem it wise to avoid this topic, presumably for the reason that concerning it so little is known. When the wise are silent it is hazardous, even foolish, for the ignorant to speak. Yet surely the editor is right in deciding that, in a book of this kind, there must be an attempt to present a chapter with this heading. It remains to be seen whether or not he was sagacious in his selection of its contributor. He who now writes seeks forgiveness for his temerity not to say impudence, and dares to express the hope that profound dissatisfaction with what he has written will provoke the better qualified to produce an infinitely preferable version.

COMPLEXITY OF STRUCTURE AND MULTIPLICITY OF FUNCTIONS

The bearing of the complexity of the structure and the multiplicity of the functions of the skin on the possibilities of prevention is of major importance.

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to say that prevention must remain impossible so long as the cause is not known, it is the case, surely that the greatest degree of precision in preventive action can be exhibited only when the cause or causes of the disease to be controlled are exactly known, and when the techniques of prevention attuned to the nature of the cause have been elaborated and thoroughly tested.

Preventive action could eliminate scabies from our population Our scientific knowledge of the mite, of its natural history of the mode of spread of the disease, of the means of destroying the mite and of preventing its dispersal is complete but in the case of this and of several other cutaneous diseases of like causation, preventive action is no longer a medical responsibility It has to wait upon the unleashing of social action of adequate magnitude and upon the amelioration of the physical and social environment in which the people live.

The precision of preventive action is also determined by the nature of the cause and by the usefulness of existing investigational techniques in the identification of the cause. Thus, if the cause of a given disease is a particular and unusual living organism which, in respect of morphology behaviour and associations, satisfies the criteria of the bacteriologist or parasitologist, there is always the possibility that it will be identified and that thereafter appropriate preventive measures may be devised. Manifestly it must prove to be exceedingly difficult to regard the staphylococcus, for example, as the sole causal agent operating in the production of a particular cutaneous disease, if this organism is commonly found on and in the healthy skin

Anthrax is rare and dangerous psoriasis is exceedingly common and merely distressful. Yet we can prevent the former whilst the latter remains beyond our control. The reason for this is that the cause of anthrax was found to be such as could be identified by the bacteriologist, using techniques already well exercised. When this organism was shown to be the cause, and a knowledge of its means of spread had been secured, it became immediately possible to devise appropriate preventive action. The causes of tuberculosis are known—the bacillus acting in conjunction with certain agencies in the socio-economic environment of the individual. Knowing these things, it is possible to take such action as would eliminate the tuberculous cutaneous diseases.

The cause of psoriasis, a disease of *far greater social* importance than anthrax, remains obscure for the reason that the ordinary investigational techniques now in use have failed to identify any responsible organism. The cause being unknown, preventive action remains quite impossible and all that can be done is purely empirical in nature.

In a general way there is a relation between the extent of our knowledge concerning a particular disease and the degree and intensity of public interest in it. In a community such as our own, the majority of skin diseases are such as yield physical blemish and discomfort rather than gross physical ugliness and total inefficiency They evoke embarrassment *in social relationships* rather than mortal fear in the beholder Leprosy for example, is rare in Great Britain because, even before its aetiology was known, mistaken notions relating to causation, but correct ideas concerning contagion, led to the adoption of the correct measures for limiting its dissemination. Because of its loathsomeness and because of the terror it

THE PREVENTION OF CUTANEOUS DISEASES

Everyone approaching this subject must be impressed by the complexity of skin structure and by the variety of functions that the skin discharges. It is a protective barrier shielding the rest of the body with its relatively constant internal environment, from the varied and often violent ingredients of the individual's external physical world. Its sensory functions not only relate the individual to his environment but also serve to protect the skin itself from harm. It prevents bodily dehydration allowing only some 400–500 cubic centimetres of water to escape (sweating apart) each day It successfully denies entrance to the body of many injurious liquids and noxious gases. It is an insulator and by the reflex regulation of its rich cutaneous blood supply especially in the hands and feet, and by sweat and by hair erection (in animals) active adjustments of heat loss are made. It has a minor excretory function. The steady loss of small quantities of carbon dioxide plays a part in the maintenance of the acid reaction of the skin surface. Loss of sodium chloride in the sweat is of great importance in hot climates or temperatures, but here again the skin plays a passive role. It is an organ of emotional expression and second only to the genitalia as a seat of sexual excitement. The cells of the horny layer contain various proteins and fatty substances. The whole layer is normally lubricated by sebaceous secretions having a high cholesterol content. In the skin various enzymes have been shown to be present, some containing an -SH group whilst others are skin proteinases and choline-esterases, the latter presumably being concerned in the destruction of acetyl choline liberated at cholinergic nerve-endings There is hormonal control of certain skin structures, as evidenced by the sebaceous gland changes at puberty and the pigmentary changes in pregnancy and in disease.

The skin surface normally swarms with micro-organisms, mainly inoffensive micrococci. The only pathogen that is commonly present is *Staphylococcus aureus* which, though relatively resistant to the self-disinfection of the skin must be removed with moderate efficiency by mechanical or other means, since there is no constant skin-population of such organisms. The haemolytic streptococci are rapidly destroyed, probably by the normal acidity produced by the fatty-acid content of the secretions of the skin Tissue immunity is called into play if the skin is partially or completely breached and micro-organisms gain an entry

Thus the skin is exposed to a great variety of agencies and circumstances which tend to evoke abnormality and its reactions can be various since its structure is complex and its functions and their control multiple. The greater the complexity of structure and the variety of function the greater the number and variety of mechanisms regulating function and the more constant and intimate the association between a particular system and disease-provoking agencies, the more abundant are the opportunities for the development in it of defect, derangement, and disease, and the more difficult preventive action must become It is to be expected that, in many pathological conditions of the skin the causes will be found to be multiple and the signs and symptoms varied and inconstant.

ON THE RELATION OF PREVENTION TO CAUSATION

Dermatologists are the first to acknowledge that the aetiology of a great many diseases of the skin is either unknown or very uncertain Though it is not true

signals of distress are flown. A cutaneous disease, dermatitis factitia, for example can be a herald of the sickness of the spirit of man. (*See for example*, Weiss and English, 1943 Hellier 1944 MacKenna, 1944 Lynch *et al.*, 1945 MacCormac *et al.*, 1946.)

It is here that the real difficulty in the search for causation, and in the design of preventive measures is encountered. For of the human personality of the mind, and of the emotions and of the relation of these to cutaneous abnormality we know very little. It is a simple matter in prevention to deal with *Sarcoptes scabiei*, but to probe into the complexities of a mind, in the search for causation and a clue to prevention, is beyond the ability of most. The plain fact is that the dermatologist must either be much more than a skin specialist or else find neither satisfaction nor serenity in his vocation. He must be a student of human and social biology for the living organism responsible for very many skin diseases is not a mite or a coccus but man, the patient himself being out of harmony either with his external world or else with another human being or with an organized group of such. The dermatologist, particularly he who would exhibit preventive action, must perforce be a clinician with an adequate knowledge of physiology entomology parasitology and bacteriology he must also be a social psychiatrist and possess a certain knowledge of human genetics, for clues concerning preventive action can be derived from knowledge gained in any one of these many fields.

In considerations concerning aetiology as a starting point in prevention, it is helpful to approach the subject in the following way Individuals differ among themselves in respect of their acquisitions and their experience. No given individual is ever static, in so far as his different functionings are concerned, for constantly and continuously there is attempted adjustment and readjustment between his component parts and between himself and the circumstances of his external world. Such adjustment or readjustment is not always complete or successful. The external world of the individual, in which he has his being, is ever in a state of flux and change, and the variety and potency of the disease-provoking agents therein are continually altering. The external worlds of different individuals differ more or less from each other in respect of their ingredients. This being so, it follows that one and the same individual, at different times and in different circumstances, is not always equally adjusted to his external world in respect of disease avoidance or resistance. Individuals of the same characterization, inborn and acquired, when exposed to different external circumstances, can react differently and individuals of different characterizations, when exposed to the same external circumstances, can display different reactions.

Granting this, then the cause or causes of a given pathological condition are to be sought amongst the differences between individuals in respect of characterization—for example, personality type, ethnic group, age, sex, occupation, and suchlike differentials—and between the circumstances, physical and social, of their external worlds. The search for causation, therefore, takes the form of two main questions What kind of an individual is this who suffers? What peculiar circumstance in his external world has he encountered that can be held responsible for his suffering? In the answers to these questions are to be found the guide to preventive action, for this in general terms must take the form of (1) an alteration of the

evoked leprosy was regarded as the brand of an offended deity its exhibitor was ostracized declared civilly dead and expelled from human society If all infectious and contagious diseases of the skin were as lethal and as horrible, and if they had an equally simple and straightforward causation, we should certainly know far more about them and possess far greater powers in respect of their control.

THE CONCEPT OF PLURIFACTOR CAUSATION

Coincident with the development of the machine, medical education became deeply rooted in a mechanistic philosophy This presented the view that man himself was [like] a machine, being composed of a number of interdependent and mutually adjusted component parts, each highly specialized and making its unique contribution to the well-being of the whole. Disease was a defect or derangement in one or more of these parts the fault or breakdown yielding disharmony among *the parts and therefore disease of the individual.* Diagnosis consisted in the identification of the part that was faulty therapeusis took the form of repair of the local fault and prevention came to be the avoidance of the breakdown of a part.

There is no doubt at all that this particular concept of disease has led to very considerable advances in medical knowledge and skill It has been largely responsible for the creation and development of many specialist branches. But it cannot wholly satisfy the dermatologist, for there is far too much in his domain that demands an altogether different approach. There are of course, diseases of the skin the primary lesion being in that part of the individual known as the skin, the disease being the reaction of this part of the individual to some unwelcome stimulus Scabies can serve as an example In its earliest stages, at least, this is not a disease of the total individual although there is some evidence that in a heterogeneous group living under identical conditions, there is a significant association between the level of intelligence of the individual and the probability that he will be found to be infested (Hodgson 1941*a* and *b* MacKenna, 1944) On the other hand Mellanby and his colleagues found no such association (Mellanby *et al* 1942)

There are other pathological cutaneous conditions which are components of syndromes the skin condition being a relatively unimportant item of the syndrome. Xanthoma diabeticorum and Addison s disease can serve as examples. In these the lesion of importance is not in the skin but elsewhere, in another part, in another organ or organ-system

There are, however many skin diseases in which it is not the skin that is diseased, either alone or in conjunction with other component parts of the individual It is the individual as a whole that is ill, the whole being far more than the sum total of the component parts. The individual is a unit. The integration that yields this entity is achieved through the central nervous system and the autonomic nervous and endocrine systems, and illness can be the reaction of the total individual to the components, living and non living, and to the circumstances of his total external world Disease can be disharmony between the individual and his environment. The skin can be as it were, the mast from which the

maturity—would have no marked effect upon the incidence of the condition in the population unless rigorously continued through very many generations.

Of autosomal dominant genes there are two kinds. First, there are those which are very rare and seriously disadvantageous to their possessors, in that they yield in addition to the skin condition, greatly diminished viability and reproductivity. Epiloia can serve as an example. Secondly there are those which yield a characterization not far removed from normality and which do not affect viability or reproductivity in this way. Keratodermia maculosa disseminata symmetrica palmaris et plantaris would seem to be an example. For the latter kind, the appropriate measure to be adopted for the prevention of the condition is non-propagation on the part of all those who exhibit the character. Since it is a dominant, those who possess the gene will exhibit the character and those who do not display the character do not possess the gene. Therefore, by denying parentage to the exhibitors of the character the passage of the gene from one generation to the next is blocked. Such action would quickly reduce the incidence of such a condition in the population.

Such a measure, however, would have very little effect upon the incidence of certain of the genes which are rare, lethal, or gravely disadvantageous, and which therefore diminish viability and reproductivity. Such genes eliminate themselves for if the gene slays its possessor it destroys its own path into the next generation. It might be expected, therefore, that such pathological conditions would quickly disappear. So they would in the absence of recurrent mutation. Since there are genes of this kind which prevent reproduction, and since the incidence of these conditions remains more or less constant generation after generation, it follows that fresh mutation occurs sufficiently frequently to maintain this equilibrium between elimination and frequency. This being so, there is no preventive action that can profitably be unleashed, since those with the gene are destroyed by it and, therefore, do not reproduce, and whatever is done to the affected individual of one generation cannot affect the size of the crop of the doomed that will appear in subsequent generations as a result of recurrent mutation.

There are dominant genes which have a low penetrance, that is to say that, even though they are undoubtedly present in the genetic constitution of an individual, they frequently fail to produce the character. Epidermolysis bullosa simplex would seem to be an example of such a gene. Individuals possessing this gene are often quite normal, but can beget affected offspring. In the face of such irregularity in the manifestation of the character it is impossible to suggest any reasonable preventive action.

THE ENVIRONMENT AS CAUSE

Many environmental physical agents are known to damage the skin, e.g. heat, cold, sunlight, x-rays, radio-active emanations, mechanical trauma. Against some of these agents the body develops a degree of protection, so that the gradual increase of exposure is a sufficient method of guarding against damage. In other cases preventive action must take the form of keeping the agent away from the skin—action which may vary from the gardener's glove to the elaborate insulation

characterization of the individual by such means as desensitization endocrine therapy nutritional adequacy vaccination inoculation, psychotherapy or an alteration of his appetites or habits (2) the alteration of the circumstances of his external world for example by change of habitat or milieu or by the removal from the present environment of the causal agent or (3) the alteration of both. Thus aetiology and prevention can be considered under the following headings (1) the individual as cause (2) the environment as cause (3) the interrelationship of individual and environment as cause. Such a classification is helpful, but, of course it is not strictly warranted for apart from accidental mutilations and the like, it is highly probable that, in the causation and expression of every abnormal condition, there is the interaction of an inborn inclination or proneness to develop a pathological lesion and an environmental provocation or encouragement to do so.

THE INDIVIDUAL AS CAUSE

There are a number of diseases of the skin in which the cause would seem to be purely genetic in origin and in which the manifestation of the condition is not at all, or only slightly influenced by environmental circumstances. An account of such diseases is to be found in a remarkable book by Cockayne (1933) It is to be noted that this encyclopaedic collection of skin diseases that have been reported as being inherited includes a great deal that is uncertain insufficient, and unconfirmed Nevertheless, there is much in it that is firm and secure, and it is abundantly clear that there are cutaneous diseases which are the direct expression of the genetic constitution of the individual and which become finally fixed at the moment of conception The great majority of these diseases according to the nature of the genes which are their causes, fall into the categories of autosomal and sex linked, dominant, and recessive characters For the purpose of this book there is no point in delving more deeply into the more complicated genetic phenomena. For information concerning these the reader is advised to consult the book by Fraser Roberts (1940) or that by Crew (1947)

If a particular cutaneous disease is the expression of a gene, and if there is no known method of controlling or overwhelming the influence of this gene upon the processes of development, the only means of preventing the exhibition of the disease in an individual yet to be conceived is that of preventing the transmission of the responsible gene from one generation to the next It is to be noted that prevention of this kind refers not to the present generation but to its successors.

The denial of parentage to such as exhibit a recessive character would do little to reduce the incidence of the condition in the population The reason for this is that at any time there are far more heterozygous individuals carrying the gene in question in the single dose, than there are homozygous individuals who carry the same gene in the double dose and therefore exhibit the character The heterozygote cannot be identified No one would advocate that parentage should be denied to anyone on the grounds that he or she might possibly be carrying a gene of this kind Yet it is the heterozygote, mating by chance with heterozygote, who is mainly responsible for the production of affected individuals. The denial of parentage to the actual sufferers themselves—assuming that these lived to reach

commonly used, although in certain parts of the world plant saponins are employed, especially for the washing of clothes. It is a matter of some interest to note that this world-wide use of soap has developed largely without any reference to medical considerations. It is only now when possible alternatives are being presented by the organic chemist, that serious medical consideration is being given to the properties of soap The general effect of washing is that of removing from the skin surface material derived from the environment as well as dead horny scales from the skin itself At the same time, a detergent-like soap removes fatty material to a greater or less extent. These fats are required for the maintenance of the normal healthy state of the skin, and their excessive removal leads to cracking of the skin when it dries. In addition to its detergent cleansing action soap has a specific killing action on micro-organisms. It is, however a highly selective agent, attacking Gram-negative organisms mainly and leaving staphylococci relatively unharmed. Soap solutions are alkaline (about *p*H 10 in a 1 per cent solution) and therefore tend to disturb the normal acidity of the skin surface. This is usually rapidly restored, however after removal of soap. Greater degrees of alkalinity due, for example, to excess of alkali in the soap, are, however definitely harmful.

The new rivals to soap are the synthetic detergents. All contain molecules which promote oil-in-water emulsion formation by containing groupings, some with an affinity for water some for oils and fats. As compared with soap these detergents have an advantage in that they are usually derived from non-edible sources. Their detergent action is usually more powerful than that of soap they are effective in the presence of salts and can be used in acid, neutral or alkaline solution. Their anti-bacterial effect varies according to their molecular constitution. Some are powerful killers of staphylococci and of many other organisms. They are, as a class, powerfully absorbed into a surface such as the skin, and may therefore, leave a large anti-bacterial effect after use. The potential disadvantages of the synthetic detergents as skin cleansers include the excessive removal of skin fats (which, of course, can be combated by mixing with oils and fats) and, in some cases, sensitizing effects due to human idiosyncrasy or allergy It is probable, however that when we have learned correctly to use these new substances a major advance in preventive medicine, comparable with the original introduction of soap, will have been achieved.

Sunlight and fresh air have beneficial effects, although for the present we are unable to offer a full explanation for these. Sunlight kills micro-organisms, it synthesizes vitamin D from sterols in the skin, and it produces mild erythema and tanning. In suitable dosages exposure to cool air currents produces vascular adaptations and reactions. Most individuals feel well when exposed to the combination of fresh air and sunlight. Infections of the skin especially of the coccal type, would appear to be less common in out-of-door conditions. All these statements of semi-factual information contain scientific truth as yet undefined.

For the maintenance of cutaneous health the skin surface must be protected from cold, friction, and excess radiation. It must be kept dry to avoid multiplication of fungi. The materials from which our present-day clothing is made do not possess all those qualities which we would demand. It may well be that synthetic materials, with a higher value in terms of disease prevention, will some day take their place.

in heating the high-altitude flying suit, from barrier creams to the leaden apron of the x ray worker

Chemical agents also damage the skin and with them a greater variety of effect is found. Many agents produce blistering, others merely an erythema. Oils or fat-soluble substances may primarily attack the hair follicles. There are many substances that are without effect on the intact skin but affect healing and have other violent effects on any abrasion. In considering the bodily resistance to chemicals, account has to be taken of the phenomenon of sensitization. Examples are readily found in the aromatic amines used in hair dyeing. Prevention of ill effects includes the shortening of the period of exposure (e.g. by washing after exposure, chemical neutralization, barrier creams, gloves)

For each type of fungal, bacterial or virus infection of the skin a fair amount of knowledge is available in terms of natural history, the source of infection, the mode of transfer and the portals of entry. Less is known of the mechanism of individual resistance. The commonest infections in Great Britain are due to the pyogenic cocci, *Streptococcus pyogenes* and *Staphylococcus aureus*. These cocci are found very commonly in apparently normal individuals, the streptococcus in the throat, the staphylococcus in the anterior part of the nasal cavity. The skin infection is very commonly associated with a focus teeming with organisms, with a crack in the naso-labial fold, beneath the pinna or at the angle of the mouth, with a running ear or an infected nasal sinus. In this category of skin diseases prevention must include attention given to the general health and the medical treatment of a minor lesion. The importance of nasal and throat carriage of organisms capable of causing cutaneous disease, and the possibility of eliminating them, are, for the present, subjects for active investigation

Ringworm in children constitutes a social problem. Prevention must depend partly upon personal cleanliness, partly upon education of parents and teachers, and partly upon public sanitary measures, since the opportunity for infection comes especially from delay in segregating infected persons and domestic animals, from communal washing and bathing, from the borrowing of garments and from imperfect laundry and hairdressing arrangements. Prevention here seems eminently possible if social action of sufficient magnitude is taken.

The war years revealed in the clearest possible fashion that an individual human being is in fact an ecological system. Both head infestation with lice and scabies were found to be exceedingly widespread. In the case of these parasites, social interest was sufficient to demand and to bring into being satisfactory methods of treatment and of prevention. Most parasitic diseases of this kind could be eliminated through the universal use of such agents as D D T., lethane, benzyl benzoate and Tetmosol soap, for example, if it were the determined wish of the community that these diseases should disappear

PERSONAL HYGIENE AS A PREVENTIVE MEASURE

Save in exceedingly cold climates where oil and fat are used instead, and in certain parts of the tropics where vegetable oils are used afterwards, washing with water is a universal habit. As a means of lowering surface tension soap is most

genetic intolerances, pronenesses, and diatheses may remain exceedingly difficult, if not impossible, the prevention of such diseases is often practicable, since, when once the environmental factor is known and removed or controlled, the genetic constituent of the cause can be disregarded.

INVITATION TO ADVENTURE

There can be no more attractive field in the whole of medical research than that of preventive dermatology. It is almost virginal, it is packed with problems of every kind, and there is none other that can be so readily forced to yield knowledge of the greatest value in application to human and social affairs. This invitation is extended by dermatologists especially to such as seek profitable exercise for their interests in human physiology, biochemistry, psychiatry and social medicine, since it would seem that clues to aetiology and therefore to prevention, are to be most rapidly disclosed by the instruments of these particular disciplines.

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THE PREVENTION OF CUTANEOUS DISEASES

The newer knowledge of nutrition gained during the last thirty years or so has shown beyond all reasonable doubt that many skin-disease manifestations can be nutritional in origin There are clearly defined syndromes for deficiencies of nicotinic acid and of riboflavin Less certain are other effects due to deprivation of vitamin A or of ascorbic acid Experimentation has suggested that the maintenance of capillary resistance to rupture depends upon an accessory substance found in citrous fruits but which is not ascorbic acid. In experimental animals dermatitis has been produced by specific deficiencies of unsaturated fatty acids and of certain amino acids Whether analogous effects are produced in man is not yet known Protein-deficient diets yield hepatic and cutaneous lesions. Less precise clinical findings suggest that certain of the desert and jungle sores are related to nutritional deficiencies. Furthermore in chlorosis with its iron deficiency the skin appears to become infected with uncommon ease. The relation between general metabolism and skin health is also manifest in the proneness of the uncontrolled diabetic to develop skin infections, particularly by the staphylococcus. Prevention of cutaneous diseases of nutritional origin must, of course, take the form of a repair of the diet In a community such as ours, it is the duty of the Government to make the raw materials of an adequate dietary available to all, and that of the individual and the parent, being educated, to ensure that what is eaten is that which is required for the maintenance of health and for the prevention of sickness.

INTERRELATIONSHIP OF INDIVIDUAL AND ENVIRONMENT

In health the skin is an organ commonly used in self-decoration and display in sickness it is a hoarding on which the handbills of anxiety and shame and the pleas for pity are plastered. Psychological stress would appear to be relieved when an obvious organic pathological condition can be displayed Discontinuity of the skin therefore, can provide a hole through which unhappiness can drain. The environment, mainly man made, is such that in it there is much that is out of harmony with the biological needs of great numbers of individuals, and for this reason very many skin lesions are reflections of psychological stress. Between the lesion and the underlying psychological stress there tends to be no specific relation. The same kind of lesion may be produced by a variety of psychological factors, and the same psychological factor can produce different lesions in different individuals The prevention of certain maladies—pruritus, prurigo eczema dermatitis artifacta, lichen planus, urticaria, rosacea, for example—must therefore take the form of the removal of the cause of the underlying psychological stress.

There is satisfaction to be derived from the knowledge that, in those cases in which the interaction of genetic and environmental factors is the cause of a particular cutaneous disease, the control of the environmental factor renders the genetic factor impotent. That different individuals exhibit different degrees of tolerance to the stimulus of particular physical agencies in the environment, is an established fact. In many instances this phenomenon is the display of an acquired tolerance, but in others it derives from a constitutional (genetic) difference between individual and individual. It is impossible, in the present state of our knowledge, to determine the exact genetical basis of such differences, nor is it possible to adopt genetical methods for their obliteration Nevertheless, whilst the control of the

(if in sufficient concentration) by the organisms in the place of the essential metabolite, but in this case the growth or reproduction is in no way helped. The theory backed by much experimental evidence, suggests that the sulphonamides are therefore bacteriostatic in action and similar to the biochemotherapeutic agents of the penicillin group. To describe antibiotic therapy as the treatment of a patient with either the sulphonamide or penicillin groups seems, therefore, to be both legitimate and useful.

The mode of action of the penicillin group of antibiotics on bacteria has not as yet been thoroughly determined. Fleming considers that the members of the group possess a lytic as well as a bacteriostatic power. Penicillin has certain distinct and definite advantages over the sulphonamide group of drugs, for it not only stops the growth of bacteria, but apparently also kills them, and it is therefore effective even if the natural defence protective mechanisms of the body are deficient. Penicillin also is effective in the presence of pus and of other substances which inhibit the sulphonamides and it has no anti-leucocytic action. Lastly penicillin is not toxic to the patient, and the unhappy complications of agranulocytosis, suppression of urine due to crystallization of the sulphonamide drugs in the tubules of the kidney, nausea, and vomiting and certain toxic skin reactions (*vide infra*) which may occur in sulphonamide therapy, no matter how carefully the drugs are administered, do not arise. Yet withal, penicillin is not the panacea of all infective disease since it exhibits a definite selectivity of action on the bacteria. Already however bacteriologists and mycologists have produced other antibiotics which are effective against some of the penicillin-resistant organisms, and it seems to be likely that in the future a combination of antibiotics with different antibacterial structures will furnish a therapeutic net from which fewer and fewer pathogenic bacteria will escape.

Before proceeding to describe the use of the antibiotic agents in the treatment of dermatological conditions, it is well to recall that the systemic use of certain of the antibiotics for some disease other than a skin disease may produce toxic effects upon which the dermatologist will be called to give his opinion. Because of longer and more intensive usage, the toxic effects of the sulphonamide group of drugs have been most frequently described in the medical literature, and it is only recently that it has been realized that even with penicillin, toxic skin manifestations may occur.

SULPHONAMIDE SENSITIVITY

There are several different types of hypersensitive reactions, the most frequent being cutaneous hypersensitivity. In most cases the probability of the condition being caused by hypersensitivity to sulphonamide can be traced by the history of previous administration of the drug, but in some it appears that the patient is hypersensitive *de novo* and that the reaction develops during a single course of treatment.

The most common dermatological manifestation seen in England is a discrete *papulo-erythematous* rash of variable distribution, which is associated with severe itching and a febrile reaction; the condition may be complicated by vomiting, the appearance of oedema, albuminuria, or icterus. This rash usually makes its

CHAPTER 16

MODERN TRENDS IN THERAPY

SECTION I

ANTIBIOTICS IN DERMATOLOGY

F CROXON DELLER

DURING the past decade, many of the keystones of former therapeutics—allopathic or homeopathic—have been reft in twain by the momentous discoveries of Domagk (1935) and of Fleming (1929)—to name only the leading personalities. As a direct result of their work, there has been built up a new approach to treatment of many conditions, both medical and surgical to this new advance the description of antibiotic therapy has been applied. To consider briefly the effect of these discoveries, with their consequent train of chemical and medical effort on the subject of dermatology to describe as aptly as possible the present position of dermatological therapeutics in relation to the antibiotics, and to hazard a guess at the possible future developments these are the objects of this section.

The phenomenon of antibiosis is seen in the unfavourable effects of the life process of one cell species upon that of another both species living in the same environment. The vital processes of the one species do not exterminate those of the other but they produce certain enzymes which break down the reproductivity of the other so allowing the defence mechanism of the host to engulf and destroy the unwanted and harmful bacteria. The general action of the antibiotics is not then one of a bactericide, but one leading to the production of bacteriostasis. Therefore—and this premise is of the utmost importance in dermatological therapeutics—the defence mechanism of the body must be capable of attacking the invading organisms rendered unreproductive by the antibiotics, or else the antibiotic agent must be absolutely specific in its action on the infecting organism.

Until recently the administration of the sulphonamide group of drugs was called chemotherapy and such chemotherapy was considered to be separate in many respects from the antibiotic therapy of the penicillin group Yet, if the theories of Fildes (1940) and Wood (1940) in relation to the action of sulphonamides are accepted, then the actions of both groups of anti infective agents are in all respects similar Fildes postulated that for normal growth of bacteria to occur it was necessary to have an essential metabolite playing a decisive role in the chemical processes associated with such growth. Such a metabolite, either synthesized by the organism or supplied from without was essential for growth or reproduction to occur He noticed that most bacteria utilized *para*-aminobenzoic acid and that this was the growth metabolite involved. Chemically the sulphonamides are sufficiently similar in composition to *para*-aminobenzoic acid to be utilized

later spreads to other areas, especially those exposed to light. It is thought that this type of reaction can sometimes be prevented by giving small doses of sulphonamides by mouth at the same time as using it locally In Peterkin's (*loc. cit.*) series of cases in the Mediterranean Theatre of War this type of reaction was one of those commonly observed He described the most common type of sulphonamide dermatitis as being due to light sensitization, and presenting as local oedema, with bullae and encrustations of the affected areas. A similar reaction has also been noted after the local application of penicillin ointment. Therefore, whenever local treatment with sulphonamides or other antibiotics is used, a careful watch must be kept for any sign of eczema developing round the lesion. If this is seen or suspected, the local treatment must be stopped at once and attempts at desensitization begun.

DESENSITIZATION AND TREATMENT OF SULPHONAMIDE REACTIONS

The problem of desensitization in such a case is still the subject of some dispute. Barber (1944) quoted Erskine, who emphasized the important point that toxic reactions, including various types of eruption, may be due either to allergic hypersensitiveness or to drug retention. These two types of reaction may be differentiated by Werner's test of sulphonamide excretion. In patients with allergic sensitization excretion is normal, but with drug retention it is diminished, and there may be albuminuria and evidence of hepatic damage, such as urobilinuria. In the former case Erskine showed that desensitization could be effected by continuing the drug in the same or smaller dosage, and this is desirable owing to the risk of immediate violent reactions should it be given later to a sensitized subject. With drug retention, however it is imperative that the sulphonamide treatment be discontinued, lest serious and even fatal damage to vital organs result. Erskine rightly insisted that the risk of these toxic reactions is minimized if sulphonamides are given orally for 7 days only or less.

An authoritative account of desensitization of the allergic type was given by Tate and Klorfajn (*loc. cit.*) They recommended that the patient should be given a course of sulphonamide systemically beginning with 0·125 gramme twice daily At first this dose caused a further local reaction to occur but usually it subsided in about 5 days. The dose of sulphonamide was then doubled and, once the ensuing reaction had subsided, the dosage was again increased in arithmetical progression. Eventually the patient tolerated full doses of sulphonamide (i.e. 6 grammes daily) without any reaction occurring. Once this state had been reached, it was considered that full desensitization had been achieved. During such a course careful watch must be kept on the output of urine and on the blood, in order to avoid the development of unhappy complications of suppression of urine and aplastic anaemia or agranulocytosis.

The treatment of a toxic reaction due to drug retention consists in the immediate stoppage of the drugs, the administration of copious amounts of fluid by mouth, rectally or (if there is any suppression of urine) intravenously (i.e. 6 litres of normal saline with 5 per cent glucose in 12 hours) the patient should also be given adequate doses of alkalis (i.e. potassium citrate, sodium citrate, potassium bicarbonate

appearance late in the course of treatment, usually between the seventh and the ninth days but in certain cases in which the patient has had a previous course of the drug systemically or particularly in a sensitive patient on whom the drug is used locally the rash may appear within 4 hours of a single dose. The concomitant symptoms of toxicity already described and the variegated distribution of the rash make the diagnosis easy The treatment is to stop the drug immediately and to give copious amounts of fluid with alkalis in sufficient amount, so as to render the urine alkaline in reaction The rash however may be a prelude to other serious complications and in every case it is wise to perform a total white-cell count of the blood. Peterkin (1945) stressed the importance of photo-sensitization in the production of the sulphonamide rashes and patients receiving these drugs should not be exposed to strong sunlight or to x-rays during treatment.

The next common type of drug eruption is the *maculo-erythematous* or *morbilliform eruption*. This occurs especially after the use of sulphathiazole. The macules are discrete, pinkish at first, later becoming brownish-red their distribution may be limited to the arms, thighs, and buttocks, or may spread to the whole of the body including the buccal mucosa and conjunctiva. The evolution of the rash takes about 12 hours and is usually accompanied by an appreciable degree of fever headache, and malaise, and in some cases the lymph glands may also be enlarged The differentiation from measles may be difficult but there are no associated Koplik s spots and the rash does not appear in the characteristic manner of this disease. Furthermore, there is no associated tracheitis or bronchitis. Again the treatment is to discontinue the drug and to give copious amounts of fluids. Usually the rash fades within 24 hours.

The *nodular type* of eruption is less common and usually follows administration of sulphathiazole the red nodes, which may resemble erythema nodosum appear around the elbows and knees, and on the front of the wrist The nodes develop chiefly on the fronts of the shins, but they may also involve the buccal mucosa and conjunctiva Again there is usually a rise of temperature and, in addition, the knees may become painful, red, and swollen

The differentiation from erythema nodosum may be difficult but the association of the symptoms following on a 7 or 9 days course of sulphonamide treatment, or within a few hours of the first dose in a patient who has previously received treatment of this nature, coupled with the almost immediate disappearance of the eruption once the drug is stopped makes the diagnosis clear cut.

Another type of eruption is an *erythemato-vesicular* one which occurs on areas exposed to light, especially ultra violet light or x rays. This rash starts as a fine papulo-erythematous eruption on the face and hands, is extremely irritable and is often associated with oedema

Eczematous eruption.—This type very rarely follows systemic treatment (in fact, Tate and Klorfajn (1944) never saw an example in thousands of cases), but arises from local application of the sulphonamides to the skin and may be masked by the initial dermatological condition. Usually the eruption does not appear until the local treatment has been used over a long period but it may occur as early as the fourth day especially if the patient has been exposed to the sun, ultra violet light, or x-rays. At first it is localized to the site of application and

later spreads to other areas, especially those exposed to light. It is thought that this type of reaction can sometimes be prevented by giving small doses of sulphonamides by mouth at the same time as using it locally. In Peterkin's (*loc. cit.*) series of cases in the Mediterranean Theatre of War this type of reaction was one of those commonly observed. He described the most common type of sulphonamide dermatitis as being due to light sensitization, and presenting as local oedema, with bullae and encrustations of the affected areas. A similar reaction has also been noted after the local application of penicillin ointment. Therefore, whenever local treatment with sulphonamides or other antibiotics is used, a careful watch must be kept for any sign of eczema developing round the lesion. If this is seen or suspected, the local treatment must be stopped at once and attempts at desensitization begun.

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and sodium bicarbonate, aā 15 grains (1 gramme)) in a suitable vehicle every 4 hours.

The local treatment of sulphonamide dermatitis may be extremely difficult. Peterkin (*loc. cit.*) found that wet dressings of weak lead and calamine lotion, or weak eusol or Alibour water were most satisfactory. When sepsis was present he recommended using either silver nitrate, 2 per cent, or crystal violet, 1 per cent solutions but on no account should acriflavine solution be used, as it may cause sensitization to that dye also and thus quickly intensify the sulphonamide reaction. In some cases of sepsis the careful prescription of penicillin cream will cause rapid resolution of the infection but this treatment needs most diligent watching.

PENICILLIN SENSITIVITY

Cutaneous reactions may occur with the penicillin group of antibiotics, but they are rare. The commonest is that which arises from local applications; the eruption may be due to the vehicle used but occasionally it is caused by the penicillin itself and in this case the usual toxic reaction is similar to that of a dermatitis due to poisoning with a heavy metal. Intramuscular injections of penicillin may cause urticaria, erythema, oedema, fever and abdominal colic, and these symptoms, when they occur, arise within a few hours of the initial injection. Recently O'Donovan and Klorfajn (1946) described a case of sensitivity to penicillin which occurred after the use of penicillin sprays on affected skin areas. Intramuscular injections of penicillin produced anaphylactic shock, and the external application of penicillin caused further recrudescence of local oedema and dermatitis. They showed that by giving penicillin orally they were able after a prolonged course of treatment, to desensitize the patient completely. Such reactions, however, are fortunately very rare.

ANTIBIOTIC THERAPEUTICS

Before describing briefly those dermatological conditions for which treatment with the antibiotics is of value, a word of warning must be proffered against the mere prescription of either penicillin or one of the sulphonamides or other antibiotics because to do so is fashionable. As may be realized, from the above short description of some of the toxic reactions attendant upon their use, it must be remembered that with the sulphonamides, at least, there are some positive dangers, such as agranulocytosis, aplastic anaemia and suppression of urine, with which occasionally one has to contend. *Barber (1944)* wrote, *in a critical* assessment of the worth of the sulphonamides in dermatological practice:

> In an article ... written in 1931 I said that "the discovery of an anti-streptococcal therapeutic agent ... would abolish many acute and chronic diseases." The advent of the sulphonamide compounds raised hopes that this prophecy might be fulfilled ... Nevertheless they fall short of the ideal envisaged for several reasons. *Thus whilst invaluable in acute infection by* the haemolytic streptococcus, the pneumococcus, the meningococcus and the gonococcus, they are far less potent against the less virulent strains of streptococcus and in chronic infections, and the risk of severe and dangerous toxic effects precludes their use over long periods.

As with all new methods of treatment, the use of the sulphonamide compounds has been grossly abused. They have been, and still are, prescribed without rhyme or reason for conditions in which they could do no possible good, and might well prove actually harmful or dangerous.

Regarding sensitization Barber (*loc cit*) says

> The argument involves two main considerations, namely first, whether or not the topical use of the sulphonamides is so superior to older methods of local treatment that it is justifiable to take the slight risk that sensitization of the skin to them may occur and secondly whether or not the results of sensitization may be so serious as to preclude entirely the local application of these drugs in superficial pyogenic infections ?

In prescribing antibiotic therapy it seems, therefore, logical always to try to answer these two questions before beginning the actual application. With the penicillin group of antibiotics the answers to these two questions may be relatively more simple, yet the temptation to be fashionable will remain—and must be combated. Otherwise, as Barber states, it reduces therapeutics to the level of the cure-all patent medicines, and the medical profession to that of their vendors

LOCAL TREATMENT WITH SULPHONAMIDES

There seems to be a considerable difference of opinion as to the efficacy of the sulphonamides when prescribed locally The doubt, shared by many dermatologists, as to whether the local use of these drugs is in any way superior to that of the older and simpler remedies, is a very real one. Owing to the risk of the patient developing an allergic hypersensitivity Tate and Klorfajn (*loc. cit*) stated unequivocally that topical sulphonamide therapy for skin diseases and minor injuries is unjustifiable, and should be discontinued Barber (*loc cit*) considers that it is the repeated contact of the sulphonamide with the cells of the Malpighian layer which is responsible for the production of the eczematous response. Therefore, the local application of the sulphonamide is a much greater hazard in the treatment of cutaneous diseases than in the treatment of such surgical conditions as burns and wounds. If, however it is decided that local therapy should be employed, then the use of a cream containing 5 per cent of sulphadiazine is the most suitable. Pillsbury *et al.* (1941), in a report on the treatment of impetigo in the American Army state that this cream was used routinely without any ill effects, and in their view sensitization is rare.

The balance of the evidence placed before us—especially in view of the advent of penicillin and the other antibiotics—is that the topical use of the sulphonamides is fraught with so many dangers that it is not usually worth the risks involved.

SYSTEMIC TREATMENT WITH SULPHONAMIDES

Turning now to consider the treatment of certain dermatological conditions with systemic sulphonamide, there is evidence that in certain specific conditions the treatment is of the utmost value, provided that the two questions which Barber (*loc. cit.*) asked, and which are quoted above, can be safely answered.

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> In an article written in 1931 I said that "the discovery of an anti-streptococcal therapeutic agent would abolish many acute and chronic diseases." The advent of the sulphonamide compounds raised hopes that this prophecy might be fulfilled. Nevertheless, they fall short of the ideal envisaged for several reasons. Thus whilst invaluable in acute infection by the haemolytic streptococcus, the pneumococcus, the meningococcus and the gonococcus, they are far less potent against the less virulent strains of streptococcus and in chronic infections, and the risk of severe and dangerous toxic effects precludes their use over long periods.

This means that all infective dermatological conditions must be tested bacteriologically for sensitivity before beginning treatment. Secondly penicillin is unstable unless kept at a temperature of less than 10° C., which entails storage in a refrigerator Thirdly and this is a point most often overlooked in prescribing, it is expensive for the patient. In fairness to the patient, penicillin should be prescribed only when there are definite indications for its use.

Local application

Penicillin is used either topically as a spray or a cream or an ointment, or it is given systemically by intramuscular injection. The spray must be kept stored in a refrigerator and is of most value for in-patient therapy since its application may be difficult anatomically for the patient. The ideal base for the cream has yet to be found but the most satisfactory so far is that described by Jeffrey (1945)

Arachis oil – – – – – – – –	125 millilitres
Lanette wax SX – – – – – – –	60 grammes
Water – – – – – – – – –	275 millilitres.

Heat the sterilized oil to 70° C. Add the wax. Heat the water to 60°–65° C. Add the water to the wax and oil with gentle stirring. Maintain at 65° C. for 2 hours in order to sterilize. Store in 100-gramme pots in a refrigerator until the cream is needed for use.

Somby (1946) states that a suitable ointment base has to possess many qualities it should be neutral, as any excess of alkalinity or acidity destroys the penicillin it should readily lend itself to sterilization since a contaminated ointment base also destroys penicillin sterilization should not affect its *p*H concentration It should not irritate the conjunctiva it should fairly readily take up penicillin, and also liberate it fairly readily For the present, Eucerin ointment base appears to be the most satisfactory but it is possible that Vaseline or *soft paraffin* (Petrolatum, *U.S.P* XII) will prove to be better

Systemic administration

The systemic administration of penicillin intramuscularly has certain draw backs the injections have to be given at *regular* intervals, the site of injection often remains painful for several hours and, after a few days of treatment, the thought of the next injection often has an unpleasant psychological effect on the patient.

The other objection to the use of penicillin is the possibility of producing a resistant strain of a previously sensitive organism. This is the result of inadequate dosage. Since penicillin produces few *toxic* effects, the golden rule should be that if there is a doubt as to the satisfactory dose then one should double it. In the early days of this form of systemic therapy the suggested dosage was 15,000–30,000 Oxford units given every 3 hours. There is a tendency now to use much bigger dosages of up to 200,000 Oxford units every 8 hours, the rationale being that, besides decreasing the number of daily injections for the patient, the antibiotic action of the drug is exercised upon the early mitotic forms of those bacteria which escaped the previous injection It must be remembered, however that, as

Impetigo contagiosa

Many dermatologists consider that the older methods of treatment are the most satisfactory in this condition others consider that with penicillin cream a cure can be effected with ease and no danger Martin (quoted by MacKenna, 1945) however stated that the *combined local and systemic treatment of this* condition with sulphathiazole was eminently satisfactory He suggested that the patient should receive 2 grammes of sulphathiazole thrice daily for 4 days, *with a 5 per cent sulphathiazole paste locally*

MacKenna and Cooper Willis (1945) described the comparative treatments of this condition *with microcrystalline sulphathiazole in 15 per cent suspension*, ordinary sulphathiazole in 15 per cent suspension, and lotio cupro-zincica. Their results, based on a statistical analysis of 1 118 uncomplicated cases of impetigo contagiosa, suggested that, except for the risk of sensitization (1 40), treatment with sulphathiazole, in either form, was superior to that with lotio cupro-zincica, both in results and in length of treatment necessary They further suggested that, as between the two forms of sulphathiazole, the advantage lay with the microcrystalline form.

The weight of the evidence is, however that this form of treatment should not be the first line of attack, but that it may be useful when other methods have failed

Dermatitis herpetiformis

A course of *sulphapyridine, starting with 6 grammes daily* for 4 days and following this with 0 5 gramme daily for a prolonged period, has been found by Barber (*loc cit*) and by Barling (1944) to be of some value in controlling this disease but cure—it does not.

Lupus erythematosus

The streptococcal form of this disease should receive a full course of sulphonamide therapy systemically but this must be accompanied by the most careful search for any focus of latent sepsis. When the disease is in its acute form, it seems that the patient has an extreme sensitivity to the administration of the sulphonamides therefore, he should be kept in bed under close observation and *the doses must be extremely small to start with* e.g. 0·125 gramme twice daily until one is sure that there is no danger of sensitivity appearing.

The use of the sulphonamides in the treatment of erysipelas, boils, carbuncles, and such maladies as sycosis barbae and pustular acne, seems no longer to be indicated since the treatment with penicillin is so efficient.

TREATMENT WITH PENICILLIN

With the increasing availability of penicillin the field of dermatological therapeutics has been enormously widened. There are, however certain drawbacks *which must be remembered.* First, penicillin is not of the slightest use if the lesion is not infective in origin or if the infecting organisms are insensitive to penicillin

every 8 hours for 7 days. The affected area should be splinted with firm bandaging, and heat may be applied in the form of Antiphlogistine poultices. In severe carbuncles it may be advisable to inject 200,000 units of penicillin around the edge of the infected area but this procedure is painful and a local anaesthetic must be added to the solution. The added tension caused by the amount of fluid injected is a distinct disadvantage. Its use in this manner should be reserved for severe carbuncles only. Once the boil or carbuncle has begun to discharge, it is well to surround the skin edge with penicillin cream to prevent further infection of the skin area. With this regimen few boils or carbuncles will need incision, but some surgical judgement will be necessary in assessing the advisability of this procedure.

Erysipelas.—Although this condition will respond to the administration of the sulphonamide group of antibiotics, it is also curable with penicillin therapy and, in view of the lessened risks with this form of therapy penicillin should be prescribed in doses of either 30,000 units every 3 hours or 100,000–200,000 units every 8 hours for 5–7 days.

Erysipeloid (erythema serpens).—The infecting organism, *Erysipelothrix rhusiopathiae* is sensitive to penicillin, and the routine treatment given above will usually clear up this infection in 3–5 days.

Lymphogranuloma inguinale.—Willcox (1946) reported the successful treatment of this condition, using large doses of penicillin, 40,000–60,000 units 4-hourly for 4 days. The patients were clinically cured and were fit for discharge from hospital in 6 days.

Anthrax.—The lesion of cutaneous anthrax is apparently susceptible to treatment with systemic penicillin, using the dosage scheme outlined above.

Actinomycosis.—Systemic penicillin 100,000–200,000 units every 8 hours should be given. Those cases which appear to be resistant should be treated for a period of 14–28 days before considering the case innocuous to the action of penicillin.

LOCAL TREATMENT WITH PENICILLIN

Local penicillin therapy employing either the spray an ointment, or the cream vehicle, is useful in the following conditions, provided that the infecting organism is sensitive to its action.

Principal Indications

Staphylococcal perifolliculitis of the thigh and of other hairy areas (Impetigo of Bockhart).—In these cases the infection lies superficially and usually responds in dramatic manner to local penicillin therapy. The infected areas should be bathed in hot water and washed well with soap. After careful drying, the penicillin cream should be liberally applied night and morning. The cleansing and washing of the clothes worn must also be attended to with care.

Impetigo.—There is a good deal of controversy about the treatment of this condition, some authorities holding the view that success will follow the use of the older remedies, such as the dilute mercurial lotions. If however penicillin cream is used, it should be applied all over the face as well as to the area involved, so as to

far as dosages are concerned, we are still to some extent in the experimental stage of therapeutics. The tendency at the moment seems to be towards larger doses, longer intervals between the injections, and longer courses of treatment.

Each dose of penicillin should be prepared as near the time of injection as possible, using either sterile distilled water or sterile normal saline as the vehicle dissolving each 20 000 units in 1 cubic centimetre of the solution If the patient complains greatly of the resulting pain at the site of injection 1 cubic centimetre of 0·5 per cent Novocain may be added to the solution at the time of injection. Penicillin is also made up commercially in an oily solution of 1,250 000 units per 10 cubic centimetres for intramuscular injection. The advantage is that it is slow in action, but the rate of absorption is uncertain and the injection is painful and expensive.

Sprays and creams

The solution to be used for the spray should contain 1 000–2,000 units per cubic centimetre of sterile distilled water and the cream is usually made up to the strength of 500–1 000 units of penicillin to each gramme. Cormia and Alsever (1946) pointed out, however that the general use of a standard stock penicillin cream was unwise. They suggested that the quantitative sensitivity of the organism to penicillin should be determined and the strength of the penicillin cream varied accordingly They used strengths of penicillin which varied from 4 units per cubic centimetre up to 2,000 units per cubic centimetre and showed how inadequate strength often led to the production of a resistant strain of organism on the other hand, they showed also that in some cases too strong a concentration (1 500 units per gramme) could lead to the appearance of sensitivity of the skin to the antibiotic.

When using either the cream or the spray it is needless to point out that the container should be sterilized prior to use To spread the cream, use a freshly sterilized knife blade, spoon or spatula. No cream should be put back into the container and the lid must be replaced immediately after use

SYSTEMIC PENICILLIN

Systemic penicillin is of use in those diseases in which the sensitive organisms are too deeply embedded for the local application to penetrate. Cormia and Alsever (*loc cit*) however have stated dogmatically that the only obvious indication for the administration of systemic penicillin is in cases of severe, widespread *infectious eczematoid dermatitis* It is felt that such a statement is too sweeping a generalization but it does lend weight to the statement above that penicillin is not the panacea of all therapy

Specific indications

Boils and carbuncles—Provided that the infecting organism is penicillin sensitive, such painful lesions should be curable within 7 days with adequate systemic penicillin therapy In all cases the possibility of an underlying glycosuria must not be forgotten The dosage which is usually adequate is 100,000 or 200 000 units

Pyococcal infection of the infant's skin.—The local application of penicillin ointment or cream is often the most efficacious treatment of this condition.

Other indications

Of the many other dermatological conditions, such as fissures, seborrhoeic dermatitis, scabetic lesions, intertrigo, and lichen urticatus, in which secondary infections have occurred, the value of penicillin therapy depends on the type of the infecting organisms. The sensitivity of the organisms is the ultimate arbiter of the value of penicillin treatment.

Local applications of penicillin in cases of infected eczema require a special word of caution. There is a tendency for the lesion to flare up after the use of local penicillin, and great care and vigilance are required during such treatment. At best the therapy can only clear up the secondary infection in the lesion.

Cormia and Alsever (*loc cit*), in a critical review of the uses and abuses of penicillin in dermatology state

> Penicillin has been of little value against furunculosis, secondarily infected acne or infected sebaceous cysts, whether given topically intramuscularly or by local injection into circumscribed lesions. Temporary improvement of chronic extensive furunculosis has been followed by complete relapse even when the organisms are sensitive. General tonic measures and the use of staphylococcus toxoid are to be preferred.

OTHER ANTIBIOTICS

Dubos and Hotchkiss (1944) showed that tyrocidin had a very marked bacteriocidal effect on both Gram-positive and Gram-negative species of bacteria and that it had one other distinct advantage over penicillin. It remained stable at both body and room temperatures, and its antibiotic activity was therefore assured after application to an exposed surface They also showed that it had a much greater surface activity than has the other related antibiotic, gramicidin. This knowledge led McKee and his co-workers (1946) to experiment with tyrothricin (which contains both tyrocidin and gramicidin) in the treatment of difficult and resistant cases of pyogenic infection of the skin. The greatest impediment to treatment was the lack of a suitable penetrating vehicle, but after some experimentation they found one, the formula of which they gave as follows

Sodium mixed alkyl benzene sulphates	1 gramme
Tyrothricin	0·10 "
Propylene glycol	10 grammes
Distilled water	88·9 "

This solution was applied by inunction with the smooth end of a sterile glass rod (taking 3–5 minutes for each application) 1–5 times daily When, however there was exudation or considerable inflammation or indurations, the solution was applied as a continuous wet dressing.

prevent the spread of the disease as well as to effect a cure of the lesions. If the treatment is not successful within a week then it is better to abandon it.

Bullous impetigo.—One bulla should be nipped with sterile scissors and the exudate examined bacteriologically. If it is decided to proceed with penicillin therapy, all the bullae should be opened by snipping with sterile scissors and the penicillin cream applied carefully yet lavishly. If the patient is in hospital, the frequent use of the spray treatment will be most useful, provided that each bullous area is sprayed individually.

Blepharitis.—Most cases will respond to the application of penicillin cream twice a day, and penicillin drops should also be instilled 3 or 4 times a day into each eye. There is a tendency for severe reactions to occur in some of these cases, and the effect of the early applications should be watched most carefully. In many of the cases a concomitant course of systemic penicillin intramuscularly seems to help to cure the more chronic and resistant types.

Otitis externa.—The treatment of this condition with penicillin, locally or systemically or both, is often disappointing owing to the mixed varieties of infecting organisms. The local application can be made either with drops of penicillin solution (20 000 units per cubic centimetre) placed in the external auditory canal through a pipette, or with penicillin as a cream on sterile wool attached to an orange stick. The skin surrounding the ear should be inuncted with liberal applications of the penicillin cream to prevent spread.

Sycosis barbae.—The initial dramatic clearance of these lesions when treated with local penicillin cream is, unhappily, often marred by a relapse. In all cases there should be a course of systemic penicillin, 200 000 units every 8 hours for a period of at least 14 days. The general treatment of this distressing condition is important and it must not be neglected. Yet withal, the prognosis in these distressing cases remains an enigma.

Acne vulgaris.—The initial effectiveness of penicillin medication, either locally or systemically or both, is often of too brief duration. The cream is usually too greasy and the spray is difficult to apply satisfactorily for permanent benefits to accrue. A prolonged systemic course of 200 000 units twice a day for 3 weeks seems to be most likely to be successful. The combination of a sulphonamide preparation such as sulphadiazine 1 gramme 4 times a day with the systemic penicillin is useful in severe cases. The general condition of the patient, however, needs a great deal of consideration in planning the therapeutic attack upon this condition. There seems to be no simple remedy for this all too common disease.

Ecthyma.—The crusts must first be removed by fomentations or starch poultices and the penicillin cream applied to the resulting ulcers. Sterile dressings covered with waterproofing must then be applied.

Varicose ulcers.—In cases of heavily infected ulcers, penicillin aerosols or cream will do much to reduce the inflammatory exudate and secondary cellulitis. Those patients with much penetration and surrounding cellulitis should be given also a prolonged course of systemic penicillin (7–14 days). Yet the essence of treatment of such ulcers is rest and support to the veins.

SECTION II

PRINCIPLES OF TREATMENT

BERNARD CLIVE TATE

PERHAPS the most important trend in modern dermatological thought is the insistence on the interdependence of the skin and other organs of the body and the mind. If this is correct, then treatment must tend to become more complex and in relatively few diseases will the best results be obtained from the employment of simple remedies but here for convenience, different therapeutic methods will be discussed separately Unfortunately many observations on therapeutics inevitably lack satisfactory controls because of the innumerable differences between people and because patients always demand some form of treatment, comparison of a remedy with the efforts of Nature is rarely possible Further in sorting out the welter of publications and deciding in which directions the various branches of therapeutics are moving, personal bias cannot be excluded What seems to one observer to be of no account may to a more discerning mind appear as the start of an important trend.

DIETARY THERAPY

This section is concerned only with the curative influences of diet on skin diseases those conditions known to be due to vitamin or other deficiencies, to recognized disorders of metabolism or caused by allergy to food will not be considered here. Little serious work on the dietary treatment of skin diseases, as distinct from prevention has been possible in Europe since 1939 and there seems to be no prospect of resumption of research on any large scale.

Among the many dietetic measures which have been employed in dermatology it is difficult to discover any general trends or principles, but the following are probably the most important so far

(1) Attempts to change the anion cation ratio of the skin and/or its *p*H by acidifying or alkalizing diets.

(2) Attempts to alter the water content of the skin by manipulation of the relative proportions of protein, carbohydrate, and fat in the diet and restriction of water and salt intake.

(3) Attempts to alter sebaceous secretion by varying the kinds of fat eaten and the amounts of fat and carbohydrate in the diet.

(4) Administration of vitamins in excess of normal requirements.

(5) Administration in excess of normal requirements of substances presumed to be lost from the skin as a result of disease.

(6) Certain special diets for particular diseases.

The diseases selected for treatment were chiefly those characterized by a pyogenic infection in and around the hair follicles, and included various forms of acne, sycosis vulgaris, furunculosis, carbuncles, abscesses, folliculitis, and *ulerythema sycosiforme* (lupoid sycosis) The results were characterized by such uniform improvement as compared to the control series, that McKee *et al* decided to publish their paper on a relatively small number of cases (232 patients, of whom 112 had various types of acne vulgaris)

The very limited supplies of streptomycin have not allowed a large amount of experimental work to be carried out on tuberculous lesions It is to be hoped that this work may prove to be of value in the treatment of these dermatological problems.

CONCLUSIONS

The days of antibiotic therapy are yet young and within but a few years the whole field of dermatological therapeutics may be changed completely

It is to be hoped that the first thrill and wave of enthusiasm for the antibiotics will be tempered by an intelligent appraisal of their true worth. That their advent has been of the greatest import to therapeutics is without question provided that their limitations are appreciated The stage of experiment with the present and the future antibiotics is not yet over and all those who prescribe them in their practice are, in some small measure, partaking of those experiments. Balance and judgement are still so very necessary in our treatments.

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below normal when a rabbit previously treated with sodium bicarbonate was given hydrochloric acid or *vice versa*.

Reports on the clinical applications of acidifying or alkalizing diets are not very convincing, perhaps because these diets have been employed chiefly to correct supposed tendencies to acidosis or alkalosis rather than to produce such tendencies. Spillmann, Vérain, and Weis (1932), for instance, claimed to have found relatively wide variations in the *p*H of the blood-serum in many dermatoses and reported good results from its restoration to normal by appropriate acid or alkaline therapy. The majority of workers, however, e.g. Foerster (1931), Cresp (1932), Ginsberg (1935) have found no significant deviation from normal in either the *p*H of the serum or the alkali reserve in a wide variety of dermatoses.

Anti-retentional diets

Földes (1933) advanced the hypothesis that a number of diseases are due to general retention of water and minerals and, in response to some stimulus, to mobilization and local accumulation in a particular organ or organs of the water and minerals previously retained throughout the body. Among such conditions he includes urticaria and other allergic diseases and he also considers that water and mineral retention plays a large part in the aetiology of acne vulgaris and in susceptibility to other infections.

He claims that, by suitable diet, retentions can be prevented and the diseases to which they give rise can be either cured or greatly improved.

The dietetic principles include (a) high protein intake to promote diuresis through the action of urea and xanthines derived from protein and nucleo-protein, (b) restriction of carbohydrate, since a high carbohydrate diet promotes retention of water and minerals, (c) restriction of fat and (d) careful regulation of fluid and mineral intake. These principles seem to be generally accepted except in the case of fat restriction. Moraczewsky found that ingestion of a large amount of butter produced hydraemia and diminished water excretion. Shay, Kolm, and Fels (1945) showed that rats on a high fat diet used less water to form urine than did rats on a mixed diet, and that, when slightly dehydrated and then given water by stomach tube, the fat-fed rats excreted urine more slowly than did rats fed on mixed diets. Urbach, on the other hand, considers that a high fat diet reduces the water content of the skin.

It can easily be understood that an allergic reaction might be modified by decrease of water and minerals in the body but it is difficult to see how it could be prevented altogether unless anti-retentional treatment inhibits antibody formation. There is experimental evidence that skin infections are related to water metabolism. Kulchar and Alderson (1936) showed that involution of experimentally produced skin infection in rabbits was hastened by dehydration and that such infections were re-activated by restoration of the water balance. Retention of water could also account for the increased severity of experimental skin infections in rabbits following injection of large amounts of either glucose or saline solution of the same tonicity as observed by Pillsbury and Kulchar (1935), and for the increased susceptibility of diabetics to natural infections.

Restriction of carbohydrates has been customary for many years in cases of boils and acne vulgaris.

Acidifying and alkalizing diets

Luithlen (1911 1912a and b 1923) found that the irritability of the skin of rabbits was increased by an acidifying diet of oats or administration of acid and decreased by an alkalizing diet of green fodder or ingestion of calcium. He attributes these effects to alterations in the relative proportions of different ions in the skin the acidifying diet causing an increase of potassium and a decrease of calcium, magnesium and sodium the alkalizing diet increasing calcium and magnesium and decreasing sodium and, still more, potassium. He attached great importance to the K Ca ratio Klauder and Brown (1925) Vogt (1941) and others have confirmed these findings though Vogt attributes the changes in cutaneous irritability to alterations in the acid base balance in the skin rather than to the K Ca ratio

Sulzberger and Mayer (1931) showed that guinea pigs fed on an acidifying diet of oats were more susceptible to sensitization to arsphenamine and *para*phenylenediamine than when fed on an alkalizing diet of green fodder These results would seem to establish certain definite therapeutic principles and are worthy of further experimental and clinical trials, although other findings seem to conflict with them. The Gerson diet for instance, is largely vegetarian and alkalizing and is said to increase susceptibility to sensitization (Gerson 1935). Sandels (1929) found that in a group of 160 children the incidence of positive reactions to patch-tests with formalin tincture of arnica and adhesive plaster was reduced from 50 per cent to approximately 4 per cent after administration of hydrochloric acid milk. Mom (1942) using sodium bicarbonate as an alkalizer and ammonium chloride as an acidifier found that the acid state diminished susceptibility to contact dermatitis with 2 4–dinitrochlorbenzene whereas the alkaline state favoured sensitization. Hermannsdorfer (1927) claimed that wound healing is accelerated by an acidifying diet, and Andersen (1926) reported acceleration of healing of chronically inflamed skin ulcers. Pillsbury and Sternberg (1937) thought that experimental skin infection in dogs was milder when acidosis was developing in the animals as a result of a high fat diet.

It is not clear however that in all these investigations the quantities of protein carbohydrate and fat, and fluid intake were kept constant Variations in these might alter the water content of the skin and hence the quantity of exudate in wounds and ulcers (Földes, 1933) As pointed out by Urbach (1946), acidifying foods may have a totally different effect from administration of hydrochloric acid or ammonium chloride According to Földes, accumulation of acid substances in the body may lead to water retention whereas hydrochloric acid, calcium chloride, and ammonium chloride, when given by mouth produce diuresis.

Susceptibility of the skin to sensitization and its response to inflammatory stimuli are by no means the same thing, and the speed of wound healing has not been accurately correlated with changes in cutaneous irritability

Perhaps all the observations are correct as suggested by the experiments of Saito (1934) who found that in rabbits cutaneous sensitivity to croton oil was increased by an acidifying diet of oats, ingestion of hydrochloric acid or subcutaneous injection of sodium oxalate, but it was also increased by intravenous administration of sodium bicarbonate. Sensitivity however was reduced even

deficient absorption of vitamin A seems most unlikely. Pettler (1936) seems to have been the first to employ large doses of vitamin A for pityriasis rubra pilaris. Brunsting and Sheard (1941) demonstrated in 3 cases impaired dark adaptation which returned to normal after 150,000 *U.S.P.* units of vitamin A daily though the skin showed marked improvement in 1 case only. Porter and Godding (1945) reported 1 case with subnormal dark adaptation in which the skin almost cleared and the dark adaptation improved on 33,000 units daily, regression occurring when the vitamin was stopped. A number of similar reports confirm the value of vitamin A in pityriasis rubra pilaris though Prosser Thomas (1943) reported negative results in a case treated with 12,000 international units daily and Whittle (1943) and Gillespie (1943) failed with 100,000 units and 200 000 units daily respectively. These failures may have been due to insufficient dosage, or there may be a difference in the response of the acquired form and of the familial form of the disease. As in Darier's disease the results of dark-adaptation tests and estimations of vitamin A in the blood are not constant.

The optimal dosage of vitamin A in these diseases is uncertain; perhaps there are wide variations from case to case. Neither the vitamin A level in the blood nor the dark-adaptation test can be relied upon as a guide to the dosage.

The manner of action of vitamin A is obscure and becomes still more so if, as Stamm (1945) suggests, the skin changes which have been accepted as accompanying vitamin A deficiency are in fact due to other causes. It is also interesting to recall that striking improvement in pityriasis rubra pilaris has followed gold injections (Davies, 1936).

Treatment of cutaneous tuberculosis with vitamin D_2

This is the most dramatic and perhaps the most important advance of the century in the therapy of skin diseases. Charpy published his first case in 1943, and in the same year Dowling, quite independently and unaware of Charpy's work, started treating his first patient. Many reports from other authors have confirmed the value of this treatment. Hinglais and Hinglais (1941) reported serious dietetic deficiencies in occupied France, especially of calcium, phosphorus, and vitamin D and at the same time Charpy noticed an increase in the incidence and severity of lupus vulgaris. Correction of the deficiencies was without effect but, because of the known curative value of ultra violet rays, he tried large doses of vitamin D and calcium. The details of his treatment have varied, but the principle has remained unaltered, namely large doses of vitamin D_2 in alcohol by mouth. In 1944 he concluded that calcium, as in any adequate diet, was necessary but not in specially large doses. In 1946 he gave 3 doses of 15 milligrams (i.e. 600,000 i.u.) of vitamin D_2 in alcoholic solution in the first week, 2 doses in each of the next 3 weeks and then 1 dose weekly for the next 4 months, treatment being continued for 3–6 months after apparent cure. He advocates a low salt diet including ½–1 litre of milk daily and large quantities of vegetables, in fact a regimen approaching the Gerson diet. If active lesions are still present after 6 months he considers complete cure by this treatment alone to be unlikely and advocates local therapy as well, especially diathermy coagulation. He finds toxic symptoms rare, and claims to abolish them by giving alkalis even if treatment is continued. He

Barber (1939) and Scott (1944) advocate anti retentional diets for seborrhoeic conditions, but adequately controlled observations are lacking. Crawford and Swartz (1936) indeed reported improvement in cases of acne vulgaris on a high carbohydrate diet and intravenous injections of dextrose solution. Goodman (1935) noticed improvement in acne vulgaris and furunculosis from treatment by intravenous and local injections of normal saline, measures which seem to be the reverse of anti-retentional.

Alteration of sebaceous secretion by diet

Clinical observation and experiment have shown that the sebaceous glands, besides elaborating a secretion of their own may take up fats directly from the blood though according to Policard and Tritchovitch (1922) this occurs only in over-fed subjects Further the amount of sebum secreted is increased by a high carbohydrate diet (Rosenfeld, 1906 Kutznitsky 1913) It should be possible, therefore to modify both the amount and composition of sebum by diet and so to influence diseases of the pilo-sebaceous follicles There are plenty of clinical observations pointing to this possibility in particular the findings of such careful observers as Montgomery (1916) and Whitfield (1934) may be cited Properly controlled experiments in actual treatment, however are lacking and a good deal of further investigation is desirable.

VITAMIN THERAPY

The general trend in vitamin therapy seems to be to try each vitamin in turn, in amounts grossly in excess of normal requirements, in every disease which has hitherto proved difficult to cure, especially if the disease in question resembles in any way the cutaneous manifestations of a known or supposed vitamin deficiency Most of the claims made for vitamin therapy of skin diseases are based on such flimsy evidence that discussion of them would be valueless. There have been, however two outstanding advances—the treatment of Darier's disease and pityriasis rubra pilaris with vitamin A, and treatment of lupus vulgaris with calciferol

Vitamin A and dyskeratoses

The clinical and histological resemblances of certain follicular keratoses to the skin changes originally described by Pillat (1929) and Frazier and Hu (1931) as manifestations of vitamin A deficiency have led to extensive trials of vitamin A in such conditions, but in only two has undoubted success been achieved Peck and Chargin (1941) found the vitamin A level in the blood below normal in 8 out of 10 cases of Darier's disease, though the carotene content was not diminished and they obtained slow but steady improvement with oral administration of 200,000 U.S.P units of vitamin A daily Further work by Peck and others (1943) has confirmed these findings in the main but the precise relationship of vitamin A to this disease remains obscure. It is to be noted that improvement but not complete cure follows this intensive therapy and though reduced vitamin A levels in the blood and lowering of the dark-adaptation test are found more frequently than in controls, they are by no means constant. Further no case of keratomalacia seems to have occurred in association with Darier's disease so that a primary lack or

amino acids and may split and be shed as soon as formed. He suggests that an attempt was being made to build the epithelium with cystine instead of with a proportion of methionine because the ratio of sulphur in cystine and in methionine is as 5 4, and the epithelium of the controls contained about 20 per cent less sulphur than in the case investigated.

Starck (1946) reported considerable reduction of serum protein in patients suffering from pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceous and to a lesser degree in dermatitis herpetiformis. High protein intake, either by mouth or intravenously was stated to produce good therapeutic results. The possible implications of these investigations, especially those of Peters, are obvious. They may be the starting point of an important therapeutic principle and the use of amino acids, protein hydrolysates, plasma, etc. in diseases affecting extensive areas of skin merits full examination.

DRUG THERAPY

Internal therapy

Drugs have been used in dermatology in much the same way as the vitamins, that is if a drug has been thought to be beneficial in a particular condition, it has been tried in every obstinate skin disease. Inorganic arsenic, calcium, mercury bismuth, arsphenamines, gold and a host of other drugs have been tested in this way Inorganic arsenic and mercury at one time advocated in almost any skin disease, are now relatively little used, and enthusiasm for calcium has been steadily waning. Gold and bismuth remain the most effective drugs in the treatment of lupus erythematosus but the claims which have been advanced for them in other conditions lack adequate confirmation. The aetiology of lupus erythematosus is obscure and the modes of action of gold and of bismuth are completely unknown. The disease is comparatively rare so that it is extremely difficult for any single observer to appraise the relative merits of the two drugs, still more to decide which of the many different preparations of either is best. Both drugs seem to give about the same number of cures but whether these cured cases would have responded equally well to either drug is uncertain. Barber (1941) and others have adduced evidence that lupus erythematosus may be of streptococcal or of tuberculous origin, and Schwarz and Weber (1932) described a case associated with staphylococcal pyaemia yet very few publications record any attempt at aetiological classification of the disease.

MacKenna (1931) uses a simple clinical classification but even this is rather exceptional and it is therefore doubtful whether all investigators have been treating the same disease. Organized research is obviously required at a number of different centres, each investigating particularly one drug, but all employing the same clinical classification and a standardized investigation of the patients.

The organic arsenicals also seem to have found a place in the treatment of lupus erythematosus. Ravaut and Bocage (1926) reported successes with neoarsphenamine and since then a number of other arsenicals have given encouraging results. Mapharsen (oxyphenarsine hydrochloride) is the latest. Goldberg (1945) treated 21 patients with this drug and claimed uniformly good results. The dosage was

maintains that only alcoholic solutions of vitamin D_2 are efficacious. Dowling and Prosser Thomas (1946) reported a series of cases, including Dowling's original case, treated by tablets containing 50 000 i u. of vitamin D_2 starting with 150,000 i.u. daily and reducing this after varying periods to 100 000 or 50 000 i u. daily Few patients showed any sign of intolerance and those who did were able to take the lower doses. The serum calcium tends to become raised and may reach a relatively high level without clinical evidence of intolerance. *Treatment should be temporarily suspended if the serum calcium reaches 12 milligrams per 100 cubic centimetres or more*

Charpy (1946a) suggests that vitamin D_2 produces local tissue acidosis, and it should be the aim of treatment to maintain this

It is remarkable that calcification has not been observed. Perhaps the widespread calcification which has been reported after large doses of vitamin D_2 may as suggested by Holtz (1934) be due not to calciferol but to certain of its isomers.

Calciferol has also proved useful in tuberculous adenitis (Charpy 1946b Fanielle, 1946) and in Bazin's disease. Marre (1946) and Russell (1946) also report improvement in Boeck's sarcoid but their results, as well as the claims made for *vitamin D in other diseases, so far lack confirmation*

The outstanding fact remains that intensive vitamin therapy has proved curative in diseases not due to vitamin deficiency

Special diets for particular diseases

The only diets which have proved really valuable are those recommended by Gersen and Hermannsdorfer for lupus vulgaris, and with the introduction of calciferol they have become obsolete. The present-day prevalence of psoriasis in countries with strict rationing of protein and fats is a commentary on the low protein diet of Schamberg and the low fat diet of Gruetz and Buerger

Replacement diets

Peters (1945) treated two patients suffering from exfoliative dermatitis with cystine. In one male, aged 56 years the average weight of scales collected daily was 19 grammes and the protein intake was not above 50 grammes daily so the loss of epithelium accounted for about 40 per cent of the protein intake In two estimations the scales were found to contain 3 11 per cent and 3 19 per cent of cystine respectively whereas desquamating skin from the hands of patients recovering from scarlet fever contained from 2·05 to 2·68 per cent of cystine. One patient was calculated to be taking about 1 5 grammes of cystine and losing 0·52 gramme daily His condition deteriorated, oedema and ascites developed and he eventually became comatose. He was then given 1 gramme of cystine by mouth daily and 0·25 gramme of cystine hydrochloride subcutaneously daily After 3 days diuresis started and eventually complete recovery ensued The other case was of a woman whose diet had been generally deficient for several months. She recovered on 1 gramme of cystine given daily by mouth It is evident that any widespread destruction of the skin must drain protein from the body Peters suggests that owing to this drain there may be insufficient sulphur-containing amino acids for proper formation of new epithelium which will therefore be made of unsuitable

oil was used, 2 cubic centimetres being given twice daily for 3 days in 4 with a repetition of the course if necessary For inunction 5 per cent BAL in a lanoline, Lanette Wax SX and diethyl phthalate base was used. No increase in the urinary excretion of arsenic was observed after injection. Eagle and Magnuson (1946) use a dosage of 2 5–3 milligrams of BAL per kilogram of body-weight, repeated at 4-hourly intervals. They treated 88 patients suffering from arsenical dermatitis and reported an increased urinary excretion of arsenic in 11 cases. They consider that doses in excess of 4 milligrams per kilogram of body-weight produce an undue number of toxic symptoms. Neither of these, however nor other similar studies, show whether or not BAL is of any therapeutic value in arsenical dermatitis since there were no satisfactory controls. On theoretical grounds one would expect BAL to be of very limited value in arsenical, eczematous, and exfoliative dermatitis. The lewisite burn is caused by the direct toxic action of an arsenical compound on the tissues, and if the arsenic is removed before irreversible changes have occurred, recovery will ensue. In most, if not all cases, however arsenical dermatitis is an allergic phenomenon due to the interaction of an arsenical compound with an antibody fixed to the epidermal cells. This combination of chemical allergen with antibody is probably a reversible reaction, governed by the law of mass action, in which equilibrium will have been reached by the time clinical signs of dermatitis are apparent. Alterations in the rate of direction of the reaction by removing arsenic from the circulation or from the allergen-antibody compound can have little effect the cell damage has already been done. It is possible that the arsenic, having become fixed to the epidermis by the antibody then combines with the sulphydryl groups and so exerts a direct toxic action, but there is no real evidence of this. A careful study of the effects of BAL in arsenical dermatitis may however help to settle the question.

The use of BAL in gold dermatitis, bismuth stomatitis, and other heavy-metal intoxications obviously requires investigation.

It is, of course, useless to give BAL as a prophylactic against dermatitis during arsenic treatment because it will protect the SH groups of the tissue enzymes of the infecting parasite.

Anti-histamine drugs

The liberation of histamine or a closely related substance from cells damaged by an allergen-antibody reaction is one of the most important causes of the manifestation of allergic diseases, so that the discovery by Best and McHenry (1930) of histaminase raised hopes of effective treatment of these conditions even in cases in which the allergen could not be removed Unfortunately histaminase failed completely in clinical application. Staub and Bovet (1937) however when working on phenolic ethers and phenylethylenediamines discovered substances possessing an anti-histamine action, and although the earlier compounds were too toxic for clinical use these researches led to the introduction of drugs which are of undoubted value in the treatment of disease. Antergan (N-dimethylaminoethyl-N-benzyl aniline) was introduced by Halpern (1942), while Bovet and his co-workers (1944a and b) produced Neoantergan (N-p-methoxybenzyl-dimethyl-aminoethyl aminopyridine phosphate), a drug with still more potent anti-histamine properties. Pyribenzamine (N-pyridyl-N-benzyl-N-dimethylethylenediamine hydrochloride)

0·02 gramme in 4 cubic centimetres of distilled water injected intravenously twice weekly 6–16 injections being given (average 10) Improvement was said to be perceptible after the second injection Hyman (1946) reported improvement in 14 out of 20 patients and failure in 6 patients. He gave weekly injections starting with 5 milligrams and increasing by 5 milligrams up to a maximum dose of 40 milligrams for men and 30 milligrams for women He states that oxyphenarsine hydrochloride is sometimes successful when both gold and bismuth have failed it is less toxic than gold preparations but is somewhat more toxic than bismuth.

The value of neoarsphenamine in anthrax is generally accepted though it seems likely to be replaced by the new antibiotics. Organic arsenicals have also been used fairly extensively in chronic pemphigus but results seem uncertain Acetarsone (3–aminoacetyl–4–hydroxyphenylarsonic acid) has been employed by Oppenheim and Cohen (1943) in a dosage of 2 grammes spread over 3 days alternating with rest periods of 3 days, the drug being continued until 0·25 gramme per kilogram of body weight has been given or if necessary even after this point but with lower doses and longer rest intervals Because of its resemblance in chemical structure to acetarsone and its relatively slight toxicity carbarsone (paracarbamidophenylarsonic acid) has been recently tried by Little (1945) He gave 0 25 or 0·5 gramme daily for 3 days alternating with rest periods of 3 days. If improvement was slow 0 25 gramme was given twice daily for 10 days and then after a 10–day rest period the intermittent 3–day treatment was resumed

Germanin (Bayer 205 Antrypol, etc), originally introduced for the treatment of trypanosomiasis, is another drug which has been tried in a number of refractory dermatoses and affections of the mucous membranes, but its value has been proved only in pemphigus and dermatitis herpetiformis In neither condition however can it be relied upon to effect a permanent cure and its toxic properties are common knowledge.

This trial and error method of investigation is now being used with the sulphonamides, penicillin and other antibiotics It is a justifiable method provided that the toxicity and the sensitizing properties of the drug are carefully studied first. Already for instance, sulphapyridine has provided a great advance in the treatment of dermatitis herpetiformis.

In contrast with these empirical drugs two important series of compounds have recently been introduced, each designed to counteract a cause of disease. BAL (2 3–dimercaptopropanol) introduced as an antidote against lewisite has proved to be of great clinical value in the treatment of arsenical and mercurial poisoning, cadmium fume fever and zinc fume fever experiments suggest its use in poisoning with other metals According to Peters and his co-workers (1945) the toxic effect of trivalent arsenic compounds is due to their chemical combination with essential SH groups of certain cell proteins, especially the tissue enzymes of the pyruvate oxidase systems BAL however has a greater affinity than the tissue enzymes for arsenic with which it forms a stable compound which can be excreted

Carleton *et al* (1946) treated 30 patients suffering from arsenical dermatitis with BAL, 21 by intramuscular injection and 9 by inunction. For injection 5 per cent of BAL in a vehicle containing 10 per cent of benzyl benzoate in peanut

oil was used, 2 cubic centimetres being given twice daily for 3 days in 4 with a repetition of the course if necessary. For inunction 5 per cent BAL in a lanoline, Lanette Wax SX and diethyl phthalate base was used. No increase in the urinary excretion of arsenic was observed after injection. Eagle and Magnuson (1946) use a dosage of 2·5–3 milligrams of BAL per kilogram of body weight, repeated at 4-hourly intervals. They treated 88 patients suffering from arsenical dermatitis and reported an increased urinary excretion of arsenic in 11 cases. They consider that doses in excess of 4 milligrams per kilogram of body-weight produce an undue number of toxic symptoms. Neither of these, however, nor other similar studies, show whether or not BAL is of any therapeutic value in arsenical dermatitis since there were no satisfactory controls. On theoretical grounds one would expect BAL to be of very limited value in arsenical, eczematous, and exfoliative dermatitis. The lewisite burn is caused by the direct toxic action of an arsenical compound on the tissues, and if the arsenic is removed before irreversible changes have occurred, recovery will ensue. In most, if not all cases, however, arsenical dermatitis is an allergic phenomenon due to the interaction of an arsenical compound with an antibody fixed to the epidermal cells. This combination of chemical allergen with antibody is probably a reversible reaction, governed by the law of mass action in which equilibrium will have been reached by the time clinical signs of dermatitis are apparent. Alterations in the rate of direction of the reaction by removing arsenic from the circulation or from the allergen-antibody compound can have little effect; the cell damage has already been done. It is possible that the arsenic, having become fixed to the epidermis by the antibody, then combines with the sulphydryl groups and so exerts a direct toxic action, but there is no real evidence of this. A careful study of the effects of BAL in arsenical dermatitis may, however, help to settle the question.

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a homologue of Neoantergan but without the methoxy group has a similar pharmacological action

A series of benzhydryl alkylamine ethers have also been shown by Loew and co-workers (1945) to antagonize histamine and of these Benadryl (β-dimethylaminoethyl benzhydryl ether hydrochloride) has been used in treatment Quaternary ammonium derivatives of Benadryl are said to possess anti-cholinergic, as well as anti histamine properties (Loew et al 1946) and this may be an added advantage in treatment.

While there is abundant evidence that these drugs prevent the effects of histamine injected into animals or liberated as a result of an experimentally produced anaphylaxis, their field of usefulness in clinical medicine is not yet clear

Curtis and Owens (1945) used Benadryl in 18 cases of urticaria in doses of 50–100 milligrams by mouth one to five times daily and reported complete disappearance of the rash in 11 cases and amelioration in 3 but the eruption recurred when the drug was stopped. O Leary and Farber (1945) gave doses of 50–100 milligrams two to five times daily in 50 cases of urticaria. In 15 acute cases, 9 patients obtained complete relief and 5 were improved in 35 chronic cases 25 patients were completely relieved and 7 improved but in all except one the rash recurred when the drug was discontinued. Other workers have had similar results. Mild toxic symptoms, especially drowsiness, are not uncommon but they are rarely sufficiently severe to necessitate cessation of treatment.

Pyribenzamine has been employed by Baer and Sulzberger (1946) in doses of 50–300 milligrams daily in 17 cases of urticaria, 11 cases of atopic dermatitis and 28 cases of pruritus due to various causes It proved to be of great benefit in about half the cases of urticaria and in 11 of the miscellaneous assortment of pruritus but only one patient with atopic dermatitis was significantly improved No serious toxic symptoms were observed.

Apart from their anti histamine effect Benadryl and the *d*-aminopyridines do not possess identical pharmacological properties. For instance, Benadryl has an anti-spasmodic action (Loew et al 1946) whereas the *d*-aminopyridines produce contraction in the isolated ileum of the guinea pig (Bovet and Walthert 1944c).

According to Wells and his co-workers (1945) these drugs exert their anti-histamine effect by competing with histamine for the receptors for histamine This, at first sight would suggest that in some cases urticaria is not due to liberation of histamine because not all are relieved by these drugs. It may however simply be a matter of quantity

The anti histamine drugs cannot of course, prevent all the manifestations of all allergic diseases. In eczema, for instance, they may diminish the amount of exudate or they may relieve itching, but they cannot entirely prevent the epidermal oedema, for the epidermal damage is the cause and not the result of histamine liberation.

External therapy

Bactericides

The brilliant results of sulphonamide and penicillin treatment in certain bacterial infections has naturally led to the trial of these drugs by local application

in infective diseases of the skin. So great indeed has been the interest aroused that very little serious work on other bactericidal substances has been published for some years. Unfortunately neither the sulphonamides nor penicillin are suitable for local therapy except in selected cases with special precautions, because all are apt to produce sensitization when applied to the skin, and this may have grave consequences if the drug ever has to be administered systemically at a later date

Some of the older antiseptics have been given a new guise, notably mercury which, as phenylmercuric acetate, nitrate, or chloride, constitutes the active ingredient of a number of proprietary remedies against both bacterial and fungous infections. Byrne (1947) points out that the presence of organic protein matter diminishes the bactericidal properties of these organic mercurials far less than those of inorganic salts of mercury and he reports excellent results in 500 cases of fungous diseases of the skin and pyodermias. Unfortunately there is no satisfactory control series of similar cases, a serious criticism of this and many similar reports.

Meleney *et al.* (1946) reported on the bactericidal effect of Furacin (5-nitro-2-furaldehyde semicarbazone), one of a series of furans derived from oat bran, and a number of bacteriostatic or bactericidal substances have been extracted from other plants, but, however good these may be as antiseptics, their value in dermatology cannot be appraised until their sensitizing properties have been studied

Quinoline derivatives have been used in certain proprietary preparations for many years, the best known being Vioform (Ciba) (5-chloro-7-iodo-8-hydroxyquinoline) and Quinolor (Squibb), a mixture of 5-chlor 8-hydroxyquinoline, 7-chlor-8-hydroxyquinoline and 5 7-dichlor-8-hydroxyquinoline. These drugs, particularly Quinolor have gained a considerable reputation in infective conditions of the skin, especially in sycosis barbae. Sterosan (5 7 dichlor 8-oxyquinaldin), manufactured as a 5 per cent ointment and as a 5 per cent dusting powder was introduced by W Jadassohn in 1944 Excellent results have been recorded from its use in pemphigus neonatorum and in impetigo by Hotz and Frutiger (1944). It is usually assumed that these drugs produce their beneficial effects by virtue of their bactericidal action, but this seems doubtful as they are also sometimes of use in other skin diseases, such as psoriasis and chronic eczema, presumably not of infective origin. Their employment in dermatology merits much further study

Fungicides

Most of the fungicides used in industry and in food preserving have been tried in dermatomycoses, but for clinical use the majority have proved either too irritating or too apt to produce sensitization. The most interesting development is the use of naturally occurring fungicidal fatty acids which were introduced to therapeutics through a study of possible fungicidal agents in sweat. Peck and Rosenfeld (1938) were the first to show that, *in vitro* certain fatty acids, especially propionic, undecylenic, and caprylic acids, inhibited the growth of common dermatophytes in very high dilutions. The *in vitro* fungicidal and fungistatic action of these acids has been confirmed by numerous observers. According to Wyss, Ludwig, and Joiner (1945) their activity increases with chain length within the limits of solubility The clinical use of these acids and their salts has already

given very encouraging results, though it seems unlikely that they will entirely supersede the older fungicidal remedies Keeney and his co-workers (1944) found that a propionate-propionic acid ointment and an undecylenate-undecylenic acid ointment gave roughly the same clinical results in tinea pedis, but the propionate propionic acid ointment proved superior in its fungistatic effect on *Trichophyton mentagrophytes* and in bacteriostatic action on *Staphylococcus aureus* (coagulase positive) and β-haemolytic streptococci (Group A). Sulzberger Shaw and Kanof (1945) found both sodium propionate powder and undecylenate-undecylenic acid powder superior to boric salicylic acid powder as prophylactics with a preference for undecylenate-undecylenic acid powder which also gave better results in treatment. In a later study Sulzberger and Kanof (1946) again found undecylenic powder the best prophylactic. These tests of Sulzberger *et al* were obviously carried out with great care, but unfortunately diagnosis was not confirmed microscopically The object, however was to find an effective method of combating intertriginous dermatoses, the majority of which would be fungous infections, in the armed Forces. The authors do not claim that these fatty acid preparations act more rapidly or produce more cures than do other fungicides, but that they are less apt to cause sensitization or irritation and are therefore better suited for long continued use in prophylaxis or for mass treatment by relatively inexperienced persons.

Shapiro and Rothman (1945) used 20 per cent zinc undecylenate and 5 per cent undecylenic acid in a vanishing-emulsion base (pH 6 5) in 150 cases of dermatophytosis, all proved by direct microscopic examination or culture. In 113 cases of foot infection clinical cure was obtained in 86 per cent in 4 weeks. Relapses occurred but could be avoided by continued use of the ointment Good results were obtained irrespective of the clinical type of lesion In 9 cases of tinea circinata cure was obtained in 3 in which *Microsporon audouini* infections were present but it is well known that infection of the glabrous skin with this organism yields readily to many weak fungicides and may die out spontaneously Of 11 patients with tinea capitis caused by *M audouini* 3 were cured Keeney (1946) and his co-workers (1945a and b) found 10 per cent sodium caprylate ointment to be superior to the other fatty acid ointments in fungous infection of the feet. It also has a moderate bacteriostatic effect against *Staph. aureus* and β-haemolytic streptococci.

To decide what are the best vehicles for applying these remedies, further research is required For prophylaxis, powders have a very great practical advantage. Among others, the following formulae have been used

Powders

Zinc undecylenate	20
Undecylenic acid	2
Talc	78
Calcium propionate	15
Zinc propionate	5
Talc	80

Ointments

Undecylenic acid	5
Triethanolamine	3
Zinc undecylenate	18
Propylene glycol	10
Carbowax 1,500	19
Carbowax 4,000	30
Distilled water	15

Caprylic acid	10
Sodium hydroxide	2·45
Diethyleneglycol mono-ethyl ether	3
Carbowax 6,000	47·5
n-Propyl alcohol	10
Zinc caprylate	5
Water	22·05

A glance at these specimen ointment formulae reveals one danger namely that in the search for an elegant or easily applied preparation, there is introduced the risk of sensitization to an ingredient of the vehicle. The fatty acids themselves, and the salts used, seem to be remarkably safe in this respect, which, as Sulzberger and his colleagues point out, constitutes the chief advantage of this form of treatment.

Treatment of dermatomycosis by methods designed to alter the pH of the skin is, of course, not new Marchionini (1929) urged that all fungicidal measures should be supported by treatment with acid and he claimed to have cured 23 out of 26 cases of infection of the feet with acid alone. He used 0·4 per cent concentrated hydrochloric acid in 70 per cent alcohol, painted on several times daily This method deserves further investigation as hydrochloric acid itself though irritant in strong solution, is incapable of producing sensitization

Rothman's (1945) discovery that adult human hair contains a fatty acid which is fungistatic for *M audouini* in concentrations of from 0·000? per cent to 0·001 per cent affords a logical explanation for the spontaneous cure of microsporon infections of the scalp at puberty The fatty acid seems to be C_7–C_{11} in chain length, probably C_9. This opens up new therapeutic possibilities which so far however have not been exploited, as no method has been devised of introducing the acid into the hair follicles or of inducing the child's skin to manufacture the acid in sufficient quantities.

Sarcopticides and Insecticides

The enormous increase in both scabies and pediculosis as a result of war conditions stimulated the search for better sarcopticides and insecticides. Already Kissmeyer (1937) had re-introduced benzyl benzoate, the active principle of balsam of Peru and storax, for scabies, and this became the standard remedy in most British Public Health Clinics and in the armed Forces. Kissmeyer used *iso*propyl alcohol as the vehicle, but equally good results can be obtained with ethyl alcohol or with a watery emulsion. A number of other remedies were introduced in the early days of the war but according to Mellanby Johnson, and Bartley (1942)

only two sulphur ointment (10 per cent) and benzyl benzoate, are satisfactory and for self medication sulphur ointment was preferred tetraethylthiuram monosulphide (Tetmosol) introduced by Gordon and Seaton (1941) was not included in this study It is doubtful however whether Tetmosol will prove a serious competitor to sulphur ointment and benzyl benzoate in the treatment of scabies, as the relapse rate and the incidence of dermatitis appear rather high (Clayton, 1943 and others) but, incorporated in soap it has given encouraging results as a prophylactic.

The idea first originated in animal experiments by Gordon and his colleagues (1944) with *Notoëdres* Further experiments confirmed the value of Tetmosol soap as a prophylactic against *Notoëdres* infection in rats, showed a fairly high sarcopticidal value in scabies and a relatively low incidence of sensitization in man (Gordon *et al.*, 1944) Bartley Unsworth and Gordon (1945) observed the incidence of scabies in a closed community of 400 persons over 31 weeks during the last 13 of which 5 per cent Tetmosol soap was substituted for ordinary toilet soap During the first 18 weeks the incidence of scabies rose from 4 per cent to 9·2 per cent, 21 new cases being reported, while during the last 13 weeks when Tetmosol soap was used the incidence fell from 9 2 per cent to 0 5 per cent, only one new case occurring, and that was in the earlier part of the time when the soap was in use. Mellanby (1945) carried out experiments in a mental hospital where the incidence of scabies was high Half the inmates were issued with ordinary soap and half with Tetmosol soap After 6 weeks there was a great reduction in the incidence of scabies among those using Tetmosol soap, whereas the incidence increased in the control group

Of the insecticides in common use against pediculi, D D T (dichlor-diphenyl trichlorethane) has proved to be the most effective so far It can be used in a powder or in a 2 per cent emulsion (Scobbie, 1945 Frazer 1946) or for body lice, it can be impregnated in clothing. Lethane has proved useful in pediculosis capitis but Blackstock (1944) considers it inferior to benzyl benzoate emulsion, which he says not only destroys the lice, but also loosens the nits.

Eddy (1946) introduced a mixture of benzyl benzoate benzocaine, and D D T as a combination treatment for pediculosis and scabies, but it is likely to have only a very limited application in civilian practice The addition of benzocaine as an ovicide is of doubtful value for it is apt to produce sensitization and the effects of D D T persist long enough to destroy newly hatched larvae.

It should be noted that D D T is not effective against scabies (Hellier 1945 Franks and Dobes, 1946)

The possible clinical uses of Gammexane, the *gamma* isomer of hexachlorcyclohexane, have not been studied sufficiently for it to be compared with D.D T and other insecticides, but experiments suggest that it may be still more effective. (Its properties are briefly discussed in a Leading Article 1946)

LOCAL CHEMICAL TREATMENT OF NEOPLASMS

Cameron used sodium bicarbonate in 16 cases of rodent ulcer either as a saturated aqueous solution or in pastes or in 15 per cent and 30 per cent ointments. There

were two failures and one patient died from another cause before treatment was complete. Four ulcers remained cured after 5 years, 1 after more than 3 years and 3 after 1 year. The duration of treatment varied from 10 days to 10 months, although one lesion was treated for 2½ years. In other cases the growth seemed to be arrested. Cameron considered solutions and pastes to be more effective than ointments.

Culp, Magid, and Kaplan (1944) reported successful treatment of condyloma acuminatum with a 25 per cent suspension of podophyllin in mineral oil. Their remarkable results have since been amply confirmed. The original technique has been modified in a number of ways by different observers, e.g. by the use of a 20 per cent solution in spirit or a watery suspension with tragacanth, which allow of more accurate limitation of the preparation to the warts. How long the drug should remain on for the best results is uncertain. McGregor (1945) advises removal with soap and water after 6–8 hours, whereas Cohen (1946) advises removal after 3 days. The shorter exposure would seem preferable as severe reactions can occur especially with oily suspensions, and treatment can easily be repeated if the first application fails.

Podophyllin is considered by most writers to be useless in other types of wart, but McGregor (1945) reports successful treatment of multiple plane warts of the face. (I have also successfully treated a few cases of multiple plane warts by repeated daily applications.)

Thomson (1943) instituted treatment of plantar warts by soaking for 10 minutes daily in a 3 per cent aqueous solution of formalin as a result of an accidental cure of concomitant warts in a patient who was treated with formalin for bromidrosis. The solution must be confined to the sole of the foot, as frequent contact with thinner skin elsewhere causes an appreciable incidence of dermatitis; hence the treatment is unsuitable for warts elsewhere.

These three rather remarkable chemical treatments of neoplasms probably differ in their mode of action. Formalin may act by destroying wart virus. Sodium bicarbonate is not generally recognized as a virus destructor—it can scarcely be a simple caustic in 8 per cent solution and its mode of action remains a complete mystery. King and Sullivan (1946) found that application of podophyllin to normal human or rabbit skin caused nuclear and cytoplasmic changes in the epidermis similar to those produced by colchicine. The chromatin in the nucleus became broken up in some cells giving the appearance of distorted mitotic figures, especially of the metaphase. Cytoplasmic changes noted in different cells were spongy swelling, shrinkage of cytoplasm from the cell membrane, hydrops, delicate fibrillation, and changes in staining properties. These appearances were not permanent, normal structure being re-established within 4–6 days after a single application. Condylomata acuminata, after podophyllin treatment, showed similar histological changes. Because of the resemblance of podophyllin cells to colchicine figures suspensions of colchicine in oil were tried for condyloma acuminatum and the results were superior to those obtained with podophyllin. How this peculiar effect of podophyllin and colchicine is brought about remains uncertain. Simple arrest of mitosis in the metaphase, supposed to be the action of colchicine given by injection, seems insufficient to account for the changes caused by application of colchicine and podophyllin to unbroken skin. It is

interesting that auramine, urethane, and sodium cacodylate produce changes similar to those produced by colchicine, when given by injection.

The action of all these substances obviously merits much further study not only in the treatment of warts but also in malignant growths of the skin.

Vehicles

Much has been written in recent years on the advantages of this or that vehicle for application of remedies to the skin but it is as yet impossible to lay down general principles Most work has been done on ointment bases, but many of the conclusions reached are hypothetical Maynard (1932, 1936) pointed out the value of triethanolamine for removal of ointments and oily preparations from the skin and hair and demonstrated its wetting properties when incorporated in ointments Silcock (1937) also referred to this substance. Mumford (1938) introduced a base consisting of 3 parts of liquid paraffin 2 parts of white Vaseline and 2 parts of a mixture of hexadecyl and octadecyl alcohols containing 10 per cent of phosphoric esters of the alcohols Silcock (1939) introduced a base consisting of Lanette Wax SX and soft paraffin, 15 per cent of each and water 70 per cent. (Lanette Wax SX, a proprietary preparation, consists chiefly of stearyl alcohol with about 10 per cent of partially phosphated stearyl and cetyl alcohols.)

Since then a rather voluminous literature has grown up, chiefly dealing with emulsifying agents, and a number of proprietary emulsions have appeared on the market. Another series of preparations consists of the carbowaxes, polyethylene glycols which have a greasy or oily consistence but are miscible with water Among advantages claimed for these various bases are their ease of removal with water their penetration into the skin, the readiness with which they part with water-soluble medicaments their elegance etc These advantages are, however hypothetical and there are no reliable comparisons of the therapeutic action of these bases with that of the older preparations Every disease must be considered separately and the questions must be asked whether it is desirable to remove the ointment at all whether penetration or purely surface action is required and how rapidly or slowly medicaments should be liberated from the ointment Goldsmith (1946) gives a well balanced summary of the possible indications for different types of ointment base.

Plastics and synthetic resins may find a place in dermatological therapy as vehicles for medicaments. Pijoan Worman, and Pijoan (1943) used sulphadiazine in aqueous plastics containing dimethoxy-cellulose or polyvinyl alcohol for the treatment of impetigo A disadvantage was the slow drying of the plastic film but Draeger and Pijoan (1945) claim to have overcome this by incorporating 70 cent alcohol in the preparation.

An obvious criticism of all these vehicles is that they may produce sensitization Lanette Wax SX certainly can and so can triethanolamine which is used in a number of emulsions and as a plasticizer in some of the plastic vehicles.

Barrier creams and ointments

The work on ointment bases has naturally stimulated fresh interest in the possible uses of these bases as barriers against the potential skin hazards of

industry Again, however reliable clinical assessment of their value is lacking. Most in common use are proprietary preparations and, according to Sadler and Marriott (1946), some seem to be of little value. In spite of the amount of work which has been done, it is doubtful whether there has been any improvement on refined paraffins as a protection against water-soluble irritants and on buffered soaps as protectives against oils.

BIOLOGICAL THERAPY

The advent of the sulphonamides and penicillin has focused attention on destruction of invading germs, and the possibility of immunity of the host tends to be neglected In such conditions as boils and sycosis barbae, however destruction or inhibition of the invading organism is not likely to produce permanent cure in all cases, for the follicles are bound to be contaminated again sooner or later and unless predisposing causes have been dealt with, infection will result.

Before the introduction of sulphonamides, vaccine was probably the most popular treatment for recurrent boils. Gougerot and Meyer (1925) and Barber and Forman (1933) had also claimed successful results from intradermal injection of staphylococcal vaccine in sycosis barbae. Duhig (1945) considers that the only effective treatment for recurrent furunculosis is a combination of a sulphonamide drug and an autogenous vaccine. He gives sulphathiazole or sulphadiazine up to a total of 25 grammes and follows this up with the vaccine. A combination of penicillin and vaccine therapy in sycosis barbae would be worth investigating.

Unfortunately vaccine treatment of skin diseases such as boils is largely empirical. It is commonly assumed that vaccines produce their beneficial effects, if any by raising the antibody content of the blood, but there is no evidence that humoral antibodies play any part in immunity to boils. Indeed there is no satisfactory method of measuring staphylococcal antibodies in the serum. Staphylococcal antitoxins i.e. anti-haemolysins and anti-leucocidins, which can be demonstrated in the serum in many cases of boils and other staphylococcal infections, may or may not have anything to do with destruction of the invading organisms. Ferguson Smith (1936) showed that there was no correlation whatever between the anti-haemolysin content of the serum and the clinical course of boils. Nevertheless many competent observers have claimed good results with vaccines and with staphylococcal toxoid, and these treatments will doubtless be re-investigated when enthusiasm for penicillin has waned a little.

Immunological therapy for other skin diseases of uncertain aetiology has been reported from time to time. Toma (1931) injected suspensions of scales in saline with 0·25 per cent of formol in 3 cases of psoriasis. Wrong (1933) used the same method in 10 cases with rather encouraging results. Campbell and Frost (1932) treated 50 patients with an alcoholic suspension of scales and obtained cures in 10 and improvement in 19, but Marcozzi (1933) considered that the method had no advantage over other treatments.

Biberstein and Wachtel (1946) used injections of skin extract in lichen planus. Papules were removed with a sharp spoon or curette, cut up and ground with saline in the proportion of 3 parts of saline to 1 part of solid matter kept at room

temperature for 24 hours, then placed in a water bath at 56–60° C. for 2 hours filtered through gauze and 0·5 per cent of phenol was added. Two injections of this extract each of 0·1 cubic centimetre, were given intradermally twice a week. Of 33 cases which could be followed up there were 16 cures, 8 near cures 6 were improved and there were 3 failures. Unfortunately there were no controls

These investigations on psoriasis and lichen planus were undertaken in the assumption that the diseases are caused by virus infection. Even if the results of treatment are confirmed, however it is not clear whether we are dealing with active immunization or with desensitization.

Cross-immunization has been attempted in recurrent herpes simplex and herpes genitalis by vaccination with ordinary cow-pox vaccine. Good results have been claimed by Minami and Ohmichi (1932) Foster and Abshier (1937) and Woodbourne (1941) and Katzenellenbogen (1946) considers that the method may prevent serious damage to the eyes in Behcet s syndrome. The technique employed has varied Minami and Ohmichi found one simple vaccination effective, but most observers have used repeated vaccinations.

Treatment of pemphigus vulgaris by passive immunization is reported by Grace and Hellman (1946) Citrated blood from patients who had recovered from the disease was given in two resistant cases Both rapidly improved and though both relapsed in some degree, one cleared again after further transfusion Apparently however blood from normal persons was not tried in either case.

Desensitization in allergy

The problems of immunity are intimately bound up with those of allergy If allergy is due to the formation of an antibody comparable to antibodies produced by infections, how can desensitization be achieved? Urbach (1940) distinguishes hyposensitization from deallergization The former aims at production of more antibody in the circulating blood which combines with antigen and thus spares the fixed antibody in the sensitized tissue. Deallergization on the other hand is brought about by exhaustion of antibody There is however no satisfactory evidence for this distinction desensitization is probably always achieved by exhaustion of antibody The principle is simple and the method easy if the allergen is a soluble non toxic substance such as one of the sulphonamides, acriflavine or boric acid Sufficient of the allergen is given by mouth or by injection to neutralize the antibody present but as shown by Tate and Klorfajn (1944), the combination of allergen with antibody is a reversible reaction governed by the law of mass action so that after neutralization has been achieved, administration of allergen must be continued until the allergen antibody compound has all been excreted otherwise it will dissociate when administration of allergen is stopped and resensitization will occur Shock is not a necessary concomitant of desensitization and could be avoided altogether if there were any satisfactory means of measuring the degree of sensitization i.e. the quantity of antibody present.

The severity of the allergic symptoms is a measure of tissue damage which is caused by the energy liberated by the allergen-antibody reaction the quantity

of energy liberated in this reaction varies with the active masses of the reagents. By starting with very small doses of allergen, desensitization can often be achieved without the production of any symptoms at all.

This method of desensitization is not applicable in the case of allergy to a poisonous or a relatively insoluble substance because it is impossible to introduce sufficient of the allergen to the sensitized cells to neutralize the antibody. It is, of course, essential to change the conditions which originally led up to the production of allergy; otherwise resensitization is bound to occur. Unfortunately the circumstances leading to sensitization, as in cases of the allergic diathesis, cannot always be changed.

The foregoing remarks are not intended as a survey of modern methods of treatment. Certain very important treatments such as the sulphonamides, antibiotics, endocrine and radiation therapies, and psychotherapy are dealt with elsewhere, and most of the recognized standard treatments are omitted. Only the more modern therapeutic methods which seem to have a "future" are included and that is largely a matter of personal opinion. It would be presumptuous to attempt to predict the future of dermatological therapeutics, or to suggest lines of development, but the reading of a very large number of papers which this study has entailed has given the impression that in the matter of treatment we are guilty of more loose thinking than in any other branch of medicine, and that, if progress is to be made, two principles above all others require emphasis—first, the need for more accurate diagnosis or at least, definition of the diseases we are treating, and secondly the need for more accurate controls in our therapeutic experiments.

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THE ACTION OF RADIATION ON TISSUES

The results of investigations concerning the effect of radiation on living tissue lead one to believe that, provided the intensities of irradiation remain the same, then the magnitude of the biological effect is the same whatever the wave-length. The factor which controls the effect is the amount of radiation absorbed. This view has been steadfastly held by Chaoul, and forms the basis for his method of treatment by contact therapy Prendergast (1936), quoting Chaoul's work, stresses this fact, and quotes the work of Holthusen (1939) who compared the effects of x-rays of varying hardness with the γ-rays of radium, and found that if equal doses were given (measured in r units) no qualitative or quantitative effect could be demonstrated in the degree of skin erythema, or in the effect of radiation in the development of ascaris eggs.

The hardness or softness of x-rays depends upon the wave-length of these rays the longer the wave-length, the softer the rays. The wave-length is dependent upon the kilovoltage. The depth of penetration of the rays depends upon the degree of hardness and, therefore, on the kilovoltage.

Eagleman (quoted by Prendergast, 1936) showed that morphologically the changes in tumour cells treated with x-rays and radium showed a striking similarity when the dosage given was the same. We may assume, therefore, that the effect upon the tissues will depend upon dosage only and will be independent of the degree of hardness (i.e. the kilovoltage) of the type of radiation. This fact simplifies treatment considerably The more superficial the lesion the softer will be the type of irradiation required to produce the desired result the deeper the lesion the harder must be the radiation, and filtration must be introduced. Thus the principles governing treatment by x-rays tend to become simplified and uniform. The correct dose must be administered, but the degree of hardness (i.e. the kilovoltage) of the radiation can be adjusted to the lesion to be treated. Since our primary concern is the protection of the skin a small filter is required in all but the most superficial lesions.

GENERAL CONSIDERATIONS OF X RAY THERAPY

The essential equipment for x ray therapy is a transformer capable of activating an x-ray tube at varying potentials. The transformer is connected to a shock proof x-ray tube of the hot cathode type. The areas to be treated are localized by means of cones and lead-rubber sheets.

In an attempt to standardize this mode of treatment two divisions have been made according to the kilovoltage used. Therapy given at kilovoltages below 100kV has been called low-voltage therapy This includes the grenz ray which is activated at a potential of 10 kV and Chaoul therapy which is activated by 40–60 kV Medium-voltage therapy is the second division and includes kilovoltages 100–140 kV

In order to improve the method of treatment and to eliminate its dangers, the tendency in recent years has been to utilize a filtered radiation. In low-voltage therapy aluminium up to 3 millimetres thick is used, and in medium-voltage therapy filters of varying thickness up to 0·5 millimetre of copper are used. By using these filters the very soft radiation is excluded, and in consequence, since this soft

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SECTION III

RADIATION THERAPY IN SKIN DISEASES

P H WHITAKER

RADIATION has become established as one of the most potent single remedies in dermatology Advances in the application of physical principles to irradiation and a more clear understanding of the dangers of the method, have allowed con siderable progress to be made in the standardization and rationalization of this form of therapy

The radiations utilized are those which are produced by x rays and by the alpha, beta and gamma radiations of radium. Each type of radiation has its own particular advantages and the value of each will be discussed

THE ACTION OF RADIATION ON TISSUES

We have as yet no true concept of the mode of action of radiation upon living tissues Two theories have been put forward first that changes occur in the individual cells which if prolonged lead to destruction of the cell and secondly that changes are produced in the matrix and vessels, which cause simultaneous changes in the surrounding tissue. Whether these changes are physical or chemical is not clear Vohra (1943) has reviewed the changes. The lethal effect upon the cell is observed by vacuolation of the cytoplasm, fragmentation of the nucleus and coagulative necrosis. With non lethal doses biological changes are not noticed at first, but later the cells become more granular and turbid, the proteins are con verted into simple compounds and cause visible aggregates. This latter change is reversible if the stimulus is removed The cells return to their original state and become normally translucent It is evident that normal and malignant tissues react similarly to radiation but whereas normal tissue is resistant to radiation, malignant tissue, due to its immaturity is more sensitive, and doses which are lethal to the malignant cell are sub-lethal to normal tissues.

of the band, by as much as 25 per cent at 65 kV 45 per cent at 100 kV and 78 per cent at 135 kV with 3 mm. Al filtration.

One further point on the question of increase in the total dosage by estimation of the exit dose is that, in order to limit the therapeutic action of the rays, it is advisable to decrease the kilovoltage to allow for the maximal absorption of the rays by the superficial tissues treated. It would appear that the biological effect upon tissue is produced by absorption of the rays, therefore, in the selection of kilovoltage, one must aim at maintaining the necessary intensity at the required depth, any penetration in excess of that required being unnecessary and potentially harmful.

The depth of the structures of the skin has been described by Cipollaro (1941) who states that the basal-cell area is reached at a depth of 1 millimetre, sebaceous glands at a depth of 1·5 mm. hair follicles at 3 mm., sweat glands at 3 and 4 mm., and adipose tissues below this level. Inflammation and oedema alter these measurements, but nowhere is the skin deeper than 1 cm. Now grenz rays (10 kV) are absorbed for the most part in the first 0·5 mm. of skin. *After penetrating the horny layer* approximately 70 per cent of these rays are measurable. It will be understood, therefore, that grenz rays are suitable only for the most superficial conditions. Radiations of 40–100 kV show differences in absorption of only 5 per cent at a depth of 1 mm., but at a depth of 3 mm. the difference is 10 per cent and at 6 mm. with 100 kV it is 52 per cent, while at 40 kV it is 68 per cent, a difference of 16 per cent. For the majority of skin conditions a kilovoltage of 70 will be adequate, particularly when the rays are filtered through 1 mm. Al in an attempt to produce as homogeneous a radiation as possible. The therapeutic response is about the same with all kilovoltages. It is obviously desirable to standardize therapy as much as possible and to utilize one kilovoltage for most conditions, with a fixed filter if possible. For example, in cases of acne vulgaris in which the greatest depth of the pathological process is 3 mm., treatment with 100 kV and a filter of 2 mm. Al is preferable this is the dosage advised by Desjardins (1931) Simple inflammatory lesions of the skin are better treated with 70 kV and a minimal filter of 0·5 Al.

Dosage generally will conform to the accepted standards, and for most conditions small doses are adequate Doses of 50–70 r at weekly intervals are usual, limiting the total to erythema doses over 3 months, and avoiding further radiation for at least a year This treatment will suffice for acne, neurodermatitis, psoriasis, etc., but with lesions such as plantar warts the dose must be increased, and a dose of 900–1,200 r at 100 kV with protection of the surrounding skin may be given at one sitting with good results. Similarly callosities and keratoses may be treated with as much as 1,000 r at 100 kV but the surrounding skin should be carefully protected and further treatment should not be given until all reaction has subsided (about 6 weeks after). Many keloids respond well to sub-erythema doses of 270 r repeated weekly for 3 or 4 doses. *Hypertrichosis* and hyperidrosis may be helped by doses of well-filtered radiation of 140 kV but the danger of late skin effects is so great that the writer does not feel that the treatment is justified, if given in sufficient strength to produce permanent relief A trial with 1 or 2 doses of 250 r through 3 mm. of Al monthly is worth while.

radiation is difficult to measure a more uniform dose, which is easy to calculate, can be given. Similarly the dangers of latent effects such as pigmentation and telangiectasis are minimized As a general rule the more superficial the lesion and the more acute it is, the lower will be the kilovoltage used and the lighter the filter i e. 0·5 mm Al The measurement of dosage is always expressed in r units. This international unit has been accepted universally and since it is a unit of ionization it is an absolute one unaffected by temperature or pressure. It is capable of measuring all types of radiation and it is thus possible to combine the different types of radiation without exceeding the required total dose

This unit has, of course to be allied to the biological unit which is known as the skin erythema dose and it may be estimated that with lightly filtered radiation 400 r will be equivalent to one skin erythema dose. As the kilovoltage and filtration increase—to allow the increased protection of the skin from the soft radiation —this dose will increase also Whilst defining units, the term half value may with advantage be explained This is the term utilized in comparing the intensities of radiation, i e it is the amount of filtration which when inserted in the primary beam will reduce it to half its intensity

At 60 kV (half value layer 0 7 mm. Al) a dose of 400 r in air at 30 cm distance will produce complete and satisfactory epilation of the hair This figure was stated by Andrews, Braestrup, and Heisel (1944) They stated that in the treatment of the scalps of 2,000 children complete epilation was effected with this dose without any untoward effect. This figure differs slightly from MacKee s (1938), which is 300 r It is possible that the figures of these authorities differ on account of the fact that Andrews Braestrup, and Heisel made their measurement in free air and the question of back scatter was not taken into account. When the measurements are made by means of ionization upon the surface of the skin the dose is increased, due to back-scatter from the tissues. It is quite certain however that doses of 360 r will in fact produce epilation. In a discussion at the Royal Society of Medicine of London in 1943 Hallam stated that in Great Britain we assume that 400 r is equivalent to the epilation dose and to the erythema dose Goldsmith (1939) also found by biological means that the erythema dose is 400 r

If untoward effects are to be avoided these factors call for a most careful check of dosage and correlation of the areas to be treated together with protection of the areas not to be treated. A review of the estimation of the skin erythema dose is given by Belisaro and Pugh (1942) who state that from data produced by dermatologists 385 r is considered to be the erythema dose in Australia 435 r in Great Britain and 354 r in the United States It appears therefore, that the figure of 400 r may be taken as the skin erythema dose This dose is rarely given in dermatology at a single exposure, except for the purpose of epilation for fractional treatment is the method usually employed this dose, however must be kept in mind when relatively thin areas such as the hands are treated. By an overlap of the fields or by using a kilovoltage which will cause penetration of the tissue the sum total of the treatment, allowing for the overlap, and the exit dose may approximate the skin erythema dose. Figures for this increase are provided by Andrews, Braestrup and Heisel (1944) who state that when both surfaces of the hand are irradiated the exit dose and back-scatter increase the dose in air to each surface

than 3 months, and do not give further treatment to the same skin area in less than 12 months. Do not give to any area, fractionally over a continuous period, more than 1,000 r

These figures must be accepted with reserve and are only intended as a rough guide. Absolute units are impossible to fix.

Three types of radiation require special mention, since their properties and mode of application differ a little from those of x-rays of 40–100 kV and from the α, β, and γ-rays of radium. They are grenz rays, the radiation produced from thorium X, and short-distance therapy (Chaoul contact therapy)

GRENZ RAYS

Grenz rays was the title given by Bucky (1935) to irradiation produced by a kilo-voltage of 10–14 kV This radiation which has a wave-length between ultra violet and the soft x-rays, has a limited field of usefulness. The rays are readily absorbed by the superficial layers of the skin and little reaches the blood-vessels below

Bluefarb (1944) quoting Bucky (1935) says that the properties of grenz rays differ from x-rays in that

(1) they produce an erythema readily
(2) they give greater pigmentation
(3) they do not epilate
(4) they do not penetrate deeply
(5) they cause a rapid decline in the leucocyte count, which returns to normal just as rapidly

Because of these properties they are of value in the treatment of blepharitis without causing epilation, and in the treatment of the male genitalia without any risk to spermatogenesis. Also, since their latent effect is negligible, they are of use in such relapsing conditions as psoriasis, pruritus, and seborrhoeic dermatitis. The main disadvantage of the use of grenz rays is that they are likely to cause pigmentation.

RADIATION PRODUCED FROM THORIUM X

Thorium X is a solid substance and can be prepared in the form of an aqueous solution a varnish or an ointment. It attains its half-value in 3·65 days. Its process of disintegration is rapid and in 13 days it has been reduced to 10 per cent. It emits α, β and γ radiations and will cause a good superficial skin reaction about 4 hours after application. This reaction increases in intensity for 4 or 5 days it subsides slowly and leaves a certain pigmentation of the skin. This pigmentation varies with the sensitivity of the patient, but it usually subsides completely The radiation will penetrate only 1 mm. of the tissue and the action is therefore superficial. It may cause some oedema if used round the eyelids (Nagelsmidt, 1946). It can be used as follows.

(1) As an aqueous solution—painted on. The effect is localized and easily controlled and is particularly useful near the eye.

THE RELATION OF DOSAGE AND EFFECT

In the treatment of pathological conditions of the skin one must be guided by the effect which the radiation will produce. These effects were stated by MacKee (1938) to be as follows

(1) There are structural inhibition and atrophy of the cutaneous appendages.
(2) The environment may be so modified that bacteria and fungi often encounter a less favourable medium upon which to grow From a practical point of view there is no direct effect upon the organism.
(3) Nutrition of the living cell is affected. Small doses inhibit cell function. Large doses produce cell destruction
(4) The inhibitory and destructive action is much more pronounced on young active cells than on mature and comparatively inactive cells.
(5) There is a direct or indirect anodyne and anti-pruritic effect

Practically it would appear that small doses of 50–70 r will cause some apparent stimulation of the functions of the skin 100–250 r will tend to inhibit its functions, 350–400 r will cause epilation 400 r will cause an erythema, and 900–1,200 r will cause destruction

Gross overdosage will cause destruction of the skin which will heal only with difficulty Repeated small doses over long periods will cause atrophy of the skin and telangiectasis.

MacKee further classifies the indications for treatment as follows.

(1) Removal of hair—as in hypertrichosis, naevus pilosus, sycosis, favus, tinea capitis
(2) Reducing the activity of sebaceous glands—as in comedo acne vulgaris, rosacea, seborrhoea
(3) Inhibiting the function of the sweat glands—as in hyperidrosis, bromidrosis, chromidrosis, pompholyx, hydrocystoma
(4) Indirect effect on bacteria—as in acne, etc.
(5) So-called stimulating reaction—as in acute inflammation
(6) Radiosensitivity of immature cells—ease of destruction, e.g. epithelioma angioma, mycosis fungoides.
(7) Anodyne effect in pruritus

Radiation may be applied to induce these results either *fractionally* i.e. 50–75 r at intervals, *intensively*—250–300 r at one dose, or *by concentration*—300–2,400 r at one sitting. After irradiation there will be a latent effect before the reaction appears the larger the dose the shorter the latent period, the smaller the dose the longer this period will be. The decision as to the type of treatment having been made the prescribed *dose must be rigidly adhered to* too little treatment is in effective and too much is dangerous.

In some individuals with sensitive skins even one exposure sufficient to cause a first degree erythema will result in telangiectasis, and in any patient radiation prolonged over a period in small doses will result in telangiectasis. If a full erythema dose has been given the same skin should not be irradiated even with fractional doses, in less than 3 months. Do not prolong any fractional treatment for longer

than 3 months, and do not give further treatment to the same skin area in less than 12 months. Do not give to any area, fractionally over a continuous period, more than 1,000 r

These figures must be accepted with reserve and are only intended as a rough guide. Absolute units are impossible to fix.

Three types of radiation require special mention, since their properties and mode of application differ a little from those of x-rays of 40–100 kV and from the α, β, and γ-rays of radium. They are grenz rays, the radiation produced from thorium X, and short-distance therapy (Chaoul contact therapy)

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(1) As an aqueous solution—painted on The effect is localized and easily controlled and is particularly useful near the eye.

(2) As a varnish This is easily maintained in position. Its action may be prolonged and the reaction noted during treatment

(3) As an ointment It can be applied to large areas but it is apt to spread and therefore it is not easy to localize the dose by this method

The dosage is measured in electrostatic units, 1 000 Mache units being equivalent to 1 E.S U According to Corsi (1943), the ideal cases for the use of thorium X are chronic eczema, chronic psoriasis, chronic peri-anal conditions, soft warts, and chronic interdigital conditions. Chronic peri-anal conditions respond well to small doses (e g. 300 E.S U) and peri-anal fissures are readily healed

Nagelsmidt (1946) suggests 500–1 000 E.S U in 1 c.c. of solution for eczema, and in chronic cases as much as 1 000 E.S U or 1,500 E.S U in 1 c.c. as a varnish. Doses up to 4 000 E.S U may be used in chronic cases of warts and psoriasis. For naevoid conditions x rays or radium are preferable.

SHORT DISTANCE THERAPY (CHAOUL)

This method of treatment was popularized by Chaoul in 1935 He decided that the superior results obtained by radium therapy in skin cancer were due not to any specific quality of the rays but to the physical and technical methods of application He devised a tube which would substantially reproduce a geometrical distribution of rays through the tissues, similar to those of radium, and which would give a large dose in a short period of time. He was influenced by the fact that the energy of radium although it gives a massive dose at the surface, rapidly declines in depth and in its extent over the surface In consequence a massive dose can be given to a lesion leaving the surrounding tissues little disturbed and a healthy matrix from which rapid healing takes place He obtained his results by using a focal-skin distance of 5 cm., 60 kV and a filter of 0·2 mm of copper The apparatus he devised for the production of this radiation was novel in that the anti-cathode was elongated and brought within 3 cm of the skin In this way it was possible to give a large dose in a few minutes with little inconvenience to the patient. At a distance of 3 cm., the r output per minute approximates 900–1 000 r and by means of special applicators it is possible to localize the effect to very small areas. The apparatus he devised had many advantages—it was cheap, shock-proof and very adaptable, and the applicators were so made that accurate localization could be obtained even in such areas as the inner canthus and the pinna—difficult areas even when using shock proof apparatus Chaoul who used his method mainly for malignant conditions, used a fractional method and gave 300–400 r daily until a total dose of 4 000–8 000 r had been given. The treatment was controlled by the reaction and by the degree of erythema which developed. The reaction was characterized by a purplish erythema and desquamation of the skin Provided that this was not exceeded no untoward effects were noted The apparatus was first introduced into this country by Morison in 1936 and the first results were recorded by Flood and Smithers (1939) In cases of malignancy the tendency has been to increase the individual dose and reduce the number of treatments. Because of the localized destructive effect and little damage to the surrounding tissue, rapid healing takes place, and the scar is soft and pliable The apparatus can be used

for ordinary skin therapy by increasing the distance and so covering a larger area. It has the advantage of a rather higher dosage rate than the standardized equipment.

The main advantage of the Chaoul apparatus was a little discounted in superficial malignancy when the lesion extended deeply owing to the limitation of the depth intensity healing sometimes took place but was quickly followed by recurrence. It is considered that residual cells were left in the base of the treated area and were covered by skin which had advanced rapidly from the sides. After a short interval these cells again proliferated and recurrence occurred. It would appear that more thorough treatment of the area and utilization of a higher kV and a thicker filter would eradicate this fault, and modern experience supports this view Similar treatment given with 140 kV and a 0·5 mm Cu filter gives improved results with less frequency of recurrence. The treatment should, however be limited to very superficial neoplasms, such as basal-celled carcinoma, plantar warts, keratoses, and naevoid growths.

THE TREATMENT OF INFLAMMATORY LESIONS

Desjardins (1939a) states that acute inflammations show a rapid change when subjected to radiation. He believes that this outstanding effect is due to destruction of the leucocytes and liberation of their enzymes and antibodies. These protective substances are apparently more effective when liberated after radiation than when contained in their cell. Similarly in chronic lesions, the more sensitive lesion is the one which has considerable leucocyte infiltration, and the most resistant lesion is that in which connective tissue elements predominate. This belief is substantiated clinically by the fact that lesions of short duration are much more sensitive to radiation than are chronic lesions. This view is supported by Williams (1944) who attributes the changes to disintegration of the leucocytes, vasodilatation which follows radiation, and possibly a direct effect upon the organism. Piatt (1944) comes to a similar conclusion and states that the advantages of radiation are that it does not interfere with any other method of treatment. Arliro (1945) dealt with the subject in some detail. In his opinion the most sensitive organism is the *Staphylococcus aureus* and the most resistant is the haemolytic streptococcus. The success of treatment depends upon the state of inflammation, the amount of leucocytic content, proliferation of the fibroblast, and the infective agent. For abscesses and superficial lesions he advises 60–70 kV a distance of 16–20 cm. filtration of 0·5–3 mm. Al, dosage rate 50–200 r in acute lesions and 50–100 r in subacute lesions the amount of radiation should be controlled by the response. Blewett (1944) advocates doses of 200–300 r in the treatment of chronic pyogenic infections the exposure may be repeated in 2 3 weeks.

In acute inflammations Desjardins (1939b) advises single doses of 10–50 per cent of a skin erythema dose, repeated if necessary in 3–5 days. The more acute the inflammation the smaller will be the dose required. A considerable amount of the surrounding tissue must be irradiated so as to include as much as possible of the surrounding blood supply and circulating leucocytes. Pfahler (1943) suggests larger doses for chronic conditions for acute conditions, 50–80 r are required, and are repeated at longer intervals. He also stresses the importance of

destruction of the leucocytes and says that in acute inflammations results occur within 6–12 hours. He points out that the type of treatment should be dependent upon the clinical condition The younger the patient and the larger the area, and the more acute the disease, the smaller should be the dose. For superficial lesions soft rays only should be used either filtered through 1 mm. Al or unfiltered, and given at the first possible opportunity operation not being a contra-indication.

THE TREATMENT OF CHRONIC DERMATOSES

Treatment may be classified roughly under two headings

(1) direct radiation to the lesion
(2) indirect radiation

Since the latter is used in a small group of conditions and is not really within the province of the dermatologist, it can be dealt with briefly It comprises treatment by intensive or deep x ray therapy of 200–250 kV to the glands or spleen in such skin conditions as are associated with disorders of the reticulo-endothelial system and to the spinal cord in dermatitis associated with a pathological condition of the nervous system. There can be no doubt that in skin conditions associated with Hodgkin s disease and leukaemia x ray treatment to the primary glands and the spleen will result in amelioration of the symptoms Similarly treatment of the thyroid gland in Graves s disease and of the pituitary gland in basophilism is advantageous. Radiation has been recommended for other conditions, e.g. to the region of the thymus in psoriasis, and to the spine and sympathetic ganglia in lichen planus and essential pruritus. Many articles have been published recording good results following treatment of these latter cases. In my opinion the treatment is of questionable value there are too many factors to be considered when areas of the body are irradiated in this way and good results only occasionally occur and cannot always be repeated when desired

In prescribing treatment of chronic skin conditions, the chances of damage to the surrounding skin must be kept in mind. Every endeavour should be made to produce the maximal effect in the least possible time, and to prolong this effect for the whole duration of treatment. To achieve this a larger initial dose must be given and this should be repeated within 10 days to maintain the effect The successive doses do not necessarily have to be as large as the first one. Mac Kee (1938) quotes the figures given by Reisner (1939) showing the summation of dosage at 200 kV as in the Table.

SUMMATION OF DOSAGE AT 200 kV

Number of Irradiations	r (Each Dose)	Total Dose	Percentage
1	525	525	100
2	400	800	152
3	275	825	157
5	185	925	176
12	100	1,200	229

Thus it will be seen that successive doses should be proportionately smaller or spread out at such intervals as to allow the primary effect of the preceding dose to diminish. It would appear that an interval of 3 days should be the minimal time between doses in order to allow this decrease in degree, and one of 10 days the maximum. The rate of dosage will also affect the reaction produced, and this total over-all time must be considered in relation to the skin reaction when treatment is prescribed. Since these problems require consideration of many physical factors of irradiation rather beyond the scope of this work, the charts published by MacKee (1938) in his text-book give adequate margins of safety in prescribing dosage, and the most effective methods of treatment, and should be referred to. One must, however be guided entirely by the response of the patient to irradiation. If the condition shows a satisfactory response to the initial dose then it would be folly to alter the method of treatment. If, however the required response does not occur after the initial dose then the treatment must be altered or abandoned. Whereas failure often follows one particular choice of kV and filtration, a change to a higher kV and different filter may bring about an immediate response. The total estimated dose must not be exceeded, however

Because of the surrounding oedema and infiltration of the skin, the chronic conditions generally respond well to the higher kilovoltages and an initial kV of 100–140 is often necessary The dosage should be of the order of from 100 to 230 r repeated in 3–4 days time through a filter of 1–2 mm. Al.

Acne vulgaris

The effect in this condition is twofold the primary effect is that of inhibiting sebaceous activity and the secondary effect is that of producing in the skin a resolution of the inflammatory process. Dosage must be adequate and prolonged. A total dosage of 1,000–1,200 r should be used and be given weekly in doses of 100 r through a 1 mm. Al filter and at 100 kV If much induration is present then both the kilovoltage and the filtration can be increased with good effect, particularly if the pustules show any tendency to keloidal formation.

Neurodermatitis

Here the response is rapid particularly with regard to the subjective symptoms. The irritation is reduced after a few doses. The aim is to give small doses of about 75 r weekly until 600–700 r have been given. If large areas of the body have to be treated a scheme of alternation should be adopted, for many areas should not be irradiated at the same time care should be taken to avoid too much irradiation of one area in the treatment of a recurrence.

Psoriasis

Direct treatment to the patch is advised. Doses to the individual areas need only be small (50–75 r) repeated weekly for 3–4 doses. When treating recurrent eruptions, care must be taken to avoid irradiating too many areas. The treatment may be alternated with ultra violet light with advantage there is no physical explanation for the benefits which accrue from this combination, but there can be little doubt that the procedure is effective.

Sycosis barbae

Treatment can aim at rapid cure by epilation This is not easy owing to the contours of the part but it is always effective. Alternatively *fractional doses of* filtered radiation to aid resolution of the inflammation (e.g. 100 r twice weekly until 800 r have been given) are often effective.

Mycosis fungoides

This condition responds well to x ray therapy The dosage is variable since the lesions are sensitive, but utilization of a higher kilovoltage and filtration will help to avoid recurrence. Using 140 kV 2 mm Al, and doses up to 800-900 r complete disappearance of the lesions and rapid relief from irritation can be expected The treatment has often to be prolonged over a long period to treat all areas. Recurrences respond well to similar doses.

Verrucae

These respond well to single doses of 900–1,200 r of low voltage x ray at 100 kV with the surrounding skin protected Cipollaro (1941) advises 600 r repeated if necessary in 6–8 weeks, as being a preferable method of treatment

Fungous infections

Tinea capitis is still effectively treated by x-rays. No material advantage is to be gained by heavy filtration and a light filter is to be preferred to avoid any skin reaction. The Adamson Kienböck method with careful check is still the method of choice. Osborn Tavener and Farmer (1945) worked out the distribution of the x rays over the skull and found that a more even distribution can be obtained by the use of a plastic cap to fit the head. The Kienböck method which has stood the test of time and is so satisfactory will not however be easily overthrown.

It is very doubtful whether x ray irradiation of areas of ringworm on the *glabrous skin is of benefit some authorities advocate fractional applications of the* rays in the treatment of ringworm of the nails.

Spangler (1938) discussing chronic relatively deep-seated *fungous infections,* states that the single lesion is usually a small nodule surrounded by lymphocytes, epithelioid cells and giant cells. These nodules *increase in number until they* coalesce. Actinomycosis is a typical example. Persistent and thorough irradiation is required for these lesions. *If small in size, irradiation by radium in dosage* of 1 000–3 000 milligramme-hours is required if large, x rays in doses of *200–250 r daily until 1 500–3 000 r have been given* This treatment has frequently to be repeated. Kaplan (1944) similarly advocated 150-200 r at *7–3 day intervals until 1 500 r had been given* the radiation being filtered through 0·5 mm. of copper In the case of actinomycosis surgical drainage should be *maintained throughout the whole period of treatment.*

TREATMENT OF BASAL-CELLED CARCINOMATA

There are three possible methods of treatment of this condition namely x rays, superficial application of radium, and implantation of radon seeds or radium

needles. Magnusson (1935) comparing the results of the last two methods, states that whilst of 101 cases of basal-celled epithelioma treated with surface application, 87.1 per cent were known to be cured 3 years later of 225 cases treated by implantation, 97.3 per cent were cured (or had no signs of a recurrence) at the end of a similar period of time. He attributes the better results with implantation to the fact that it is easier by this method to deal with the deeper part of the lesion, and that by giving the dose over a longer period the effect of the radiation is enhanced. The failure of superficial application he attributes to the difficulty of maintaining the applicators in apposition to the ulcer. Regaud (1922) suggests that implantation should be reserved for those ulcers which are deeper than 15 mm., and considers that superficial therapy is better for the small superficial ulcer. Brain (1933) compares the results with filtered needles and unfiltered plaques, and is of the opinion that the results with needles are superior. Cade (1940) sums up the position as follows.

(1) Implantation is much more likely to produce complete and permanent healing than is surface or external radiation.
(2) Most of the failures occur in external radiation.
(3) Beta radiation is suitable only for very small and superficial lesions.
(4) For deep ulcers needling is the only reliable method.
(5) Combination of the methods is indicated in advanced ulcers.

In his recent book Smithers (1946) advocates x-ray therapy and gives adequate proof of the success of the method. The lesions, since they are superficial, are noted and treated early. Provided that the rays penetrate the subcutaneous tissue adequately usually only one application is necessary. A dose of 3,000 r given with the Chaoul tube (40–60 kV) is advocated. Small necrotic ulcers are similarly treated with doses of 2,000 r. If the lesion extends at all deeply then a higher kV and filtration should be used. The advantages of x-ray therapy are that it is easy to apply, cheap, and rapid, and the scars are soft and pliable. Recurrences are rare and are easily and successfully treated. Squamous-celled carcinomas are, however, better treated with radium from the start, either interstitially or superficially. Treatment with β-radiation has little part now in radiotherapy and has almost been discarded in the light of the present methods of treatment with x-rays and radium.

THE TREATMENT OF NAEVOID CONDITIONS

Naevi may be divided into two main types

(1) capillary naevus—port-wine stain
(2) cavernous angioma—haemangioma proper

The *capillary naevus* is difficult to treat. It responds poorly to radiation and does not appear to be radiosensitive. Occasionally small doses of radiation given over a long period at 2–3 month intervals do give a faint blanching of the lesions, but they are more successfully treated by plastic surgery than by any other method of treatment.

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Treatment can aim at rapid cure by epilation. This is not easy owing to the contours of the part, but it is always effective. Alternatively fractional doses of filtered radiation to aid resolution of the inflammation (e.g. 100 r twice weekly until 800 r have been given) are often effective.

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This condition responds well to x ray therapy The dosage is variable since the lesions are sensitive, but utilization of a higher kilovoltage and filtration will help to avoid recurrence. Using 140 kV 2 mm Al and doses up to 800-900 r complete disappearance of the lesions and rapid relief from irritation can be expected. The treatment has often to be prolonged over a long period to treat all areas. Recurrences respond well to similar doses

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The response of the *cavernous angioma* to radiation is different. These tumours are produced by an abnormality of the mesothelium, which results in a proliferation of the haemangioblasts. Because of their immaturity these cells are very sensitive to irradiation and often regress spontaneously at the age of 5 or 7 years.

There are two methods of treatment by irradiation which are very satisfactory

(1) superficial application of radium
(2) contact x ray therapy

For *superficial application* of radium a radium plaque, or radium or radon in the form of a mould, can be used In this way a dose of 1,500 r is given over 4 days, and repeated in 3 months time as required If the lesion is small and can be covered by a point source, 2,000 r at 2 mm skin distance may be given. This dosage will effect complete disappearance of the lesion in a short time.

By *contact therapy* a dose of 200–300 r is given and repeated at 2–3-monthly intervals The lesion must be covered and must include a small margin of normal tissue. This dose can be given in 2–3 minutes, and for this reason alone it will be seen that the treatment is very easily given particularly is it useful in the treatment of young children who can be held on a parent s knee. After treat ment, the naevus will decrease in size and will rapidly blanch. Too much treat ment must be avoided as it may cause scar formation, but if the correct dose is given no untoward effects are noticed Ap Thomas (1942), in a consideration of the results, states that 92 per cent are cured equally by radium and contact therapy Radium should be reserved for the bulky deep tissues and contact therapy for all other lesions

THE FUTURE OF RADIOTHERAPY

What can we expect of radiotherapy in the future? So standardized has the method become in the past few years, that any advance will probably now be in the mode of production of radiation. In this atomic age, with the advent of isotopes of radium—which are produced by the pile and by the cyclotron—it is very likely that eventually we shall obtain our radiation in the form of one of these *isotopes* The most recent one of these to be developed is radio cobalt, the half value life of which is 5 3 years It emits soft β-radiation and γ-radiation equiva lent to x rays produced by 1 1 and 1 3 million volts. These isotopes may produce radiation which we may find simpler to use and more beneficial in action than either x rays or radium. It may yet be possible to harness the radiation so com pletely that it can be dispersed without danger to operator or patient, but let us not forget the potential danger which will always exist in its use. The ideal would be a combination of radiation with the medicaments used so many drugs used in dermatology are compounds of the heavy metals that this may in fact be possible. We have already seen the production of radio-activity in the inert metals for short periods by the use of the cyclotron. The possibilities in this direction are enormous and will be a great advance in the treatment of diseases of the skin.

becomes hardened. Schwartz and Tulipan (1939) say that desensitization may occur under working conditions, and they have seen a contact dermatitis disappear whilst the man continued at work. They therefore, advocate that men who develop a mild dermatitis after working a few days should be given protective clothing and mild ointment and allowed to continue at work in the hope of developing immunity However these authors do not state whether the irritation is truly allergic or is due to a primary irritant effect the latter seems the more likely explanation. In general, one can say that it is impossible to rehabilitate a man with allergic sensitivity so that he can return to his original work on the other hand, he can usually do other work with impunity once he is soundly healed.

Much more important from our point of view are the effects of non-specific primary irritants such as soap and water heat and sweating, friction, etc. These may have caused the rash in the first instance, or they may lead to a relapse in a patient whose skin was previously irritated by some specific agent. The former usually occurs in people who have a constitutional eczematous tendency or in older patients who have been exposed to irritants for many years and whose skin has gradually worn out, or in whom other debilitating factors are at work. One sees this type in the elderly wool scourer who has handled alkalis since he was a boy in the aging miner working in a hot dusty pit, or the charwoman or housewife after the menopause. These patients are often difficult to cure and very hard indeed to rehabilitate as their skin has lost its resilience moreover they are usually people who like the housewife, cannot change their jobs, or else are too old to learn a new trade.

On the other hand, the patient who has developed a specific sensitivity and who can be removed from the offending work, is a more hopeful subject for rehabilitation he is usually younger and, once his skin has become soundly healed, he can undertake other types of work satisfactorily Yet how often one sees such a patient who, returning to work with his skin still red and vulnerable, breaks down even though no longer exposed to the original irritant, because his skin cannot stand up to ordinary primary irritants such as soap and water If such a patient could be put on to graded work, his skin would have a chance of getting hardened before being finally exposed to the severe trauma of full work. Workers who have been away from work for some non-dermatological reason, sometimes seem to lose their immunity through being off work and develop dermatitis on starting again, even though they had previously done the same work with impunity It would be a wise precaution if all patients who had been off work for a considerable period, from whatever cause, underwent some process of rehabilitation to break the *shock of* their return.

Physical rehabilitation of the skin is probably achieved largely by reconstitution of the horny layer so that it regains its normal resistance which is dependent, not only on increased thickness, but also on other factors such as the pH of the sweat and the composition of the secretion of the sebaceous glands. The cells *of* the deeper layers and the vessels also remain sensitive for considerable periods, even when, externally the skin appears normal, and they must be given time to settle down. These points must be taken into consideration in devising the form of rehabilitation to be undertaken by skin patients, so that the right amount of

CHAPTER 17

THE REHABILITATION OF PATIENTS SUFFERING FROM CUTANEOUS DISEASE

F F Hellier

The organized rehabilitation of skin patients is a new idea, though dermatologists have at times applied similar methods to individual cases. In this chapter the principles underlying rehabilitation and their application to skin conditions, will first be discussed a description will then be given of the work at Ragley Hall, a rehabilitation centre for skin cases set up by the British Army and the first centre of its kind finally the application of these ideas to civil practice in the future will be considered

One of the best definitions of rehabilitation was given by Crew (1946) in his report on rehabilitation in the Army The aims and purposes of rehabilitation are the maintenance or re-creation of high morale and the restoration of normal physical function The success of rehabilitation is determined by the creation and maintenance of the " will to get well on the part of the individual soldier and the physical limitations imposed upon him by the injury or illness.

It is, of course, debatable whether rehabilitation can be separated from ordinary treatment and whether it should not more properly be considered as an attitude towards treatment rather than an entity in itself but for the purpose of this discussion we may divide it into (1) physical rehabilitation, (2) psychological rehabilitation although these two are really interdependent

PHYSICAL REHABILITATION

Physical rehabilitation is easy to visualize for surgical or orthopaedic conditions, in which the tone of a muscle or the movement of a joint can be increased by physiotherapeutic exercises, but how can such methods be applied to lesions of the skin? Is it possible to improve the resistance of the skin against trauma by increasing the thickness of the horny layer or by diminishing the irritability of the papillary vessels or by altering some other mechanism in the skin? In what type of patient can we expect rehabilitation to be of value?

In answering these questions one must distinguish clearly between true allergic [illegible] In the former the patient becomes [illegible] s exposed to it, even in minute [illegible] to desensitize the patient In most of the cases in which such desensitization has been reported either the results have been partial or there has been doubt about the original diagnoses There is evidence that workers may acquire some degree of immunity against skin irritants thus new entrants into tanning works frequently get irritation until their skin

becomes hardened. Schwartz and Tulipan (1939) say that desensitization may occur under working conditions, and they have seen a contact dermatitis disappear whilst the man continued at work. They therefore, advocate that men who develop a mild dermatitis after working a few days should be given protective clothing and mild ointment and allowed to continue at work in the hope of developing immunity. However these authors do not state whether the irritation is truly allergic or is due to a primary irritant effect the latter seems the more likely explanation. In general, one can say that it is impossible to rehabilitate a man with allergic sensitivity so that he can return to his original work on the other hand, he can usually do other work with impunity once he is soundly healed

Much more important from our point of view are the effects of non-specific primary irritants such as soap and water heat and sweating, friction, etc. These may have caused the rash in the first instance, or they may lead to a relapse in a patient whose skin was previously irritated by some specific agent. The former usually occurs in people who have a constitutional eczematous tendency or in older patients who have been exposed to irritants for many years and whose skin has gradually worn out, or in whom other debilitating factors are at work. One sees this type in the elderly wool scourer who has handled alkalis since he was a boy in the aging miner working in a hot dusty pit, or the charwoman or housewife after the menopause. These patients are often difficult to cure and very hard indeed to rehabilitate as their skin has lost its resilience moreover they are usually people who like the housewife, cannot change their jobs, or else are too old to learn a new trade.

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stimulation of the horny layer is obtained to promote thickening without at the same time irritating the deeper structures.

PSYCHOLOGICAL REHABILITATION

This may be divided into diversional and purposive therapy Skin patients are not usually very ill and both in hospital and outside, experience intense boredom from enforced idleness and the long duration of their disability They become increasingly introspective, and their morale tends to deteriorate under that process so aptly described by Telling as rusting and brooding Anything which diverts their attention from themselves, and lets them employ their hands for other purposes than scratching, aids their recovery Such occupational therapy should be provided from the start and not at a later stage when the patient is said to be convalescent. Purposive psychotherapy is directed against those psychological stresses to which the skin patient is particularly prone. These may be transient—the result of external conditions—or of long duration and due to the constitutional make up of the patient himself or they may be a combination of the two The commonest factor is worry about security and loss of wages, both in the present and the future added to this is the upset of the illness and the shock of interruption of the routine of years. This anxiety is often prolonged by the slow settlement of his compensation claims, so that the man is drawing neither sickness benefit nor compensation and he sees his savings disappear and debts accumulate. Once compensation has been awarded a new factor is introduced. The man now has a certain degree of security to which he clings. He knows that having been labelled a dermatitis case he will have difficulty in getting work especially if he is unable to return to his old job. He often thinks, erroneously that once he returns to work, his compensation cannot be reinstated if he has a relapse, and so he is unwilling to abandon his one certain source of income. These difficulties frequently produce a sense of injustice and a feeling of bitterness on the part of the man, which lowers his morale still more. Other factors also play their part such as domestic worries at home or difficulties with the foreman or fellow workmen whilst in some patients the mere fact that they have something wrong with their skin produces depression anxiety and the so-called leper complex. These patients must be helped by a friendly discussion of their problems, and an attempt made to solve them this usually requires more commonsense than psychology but we shall fail to do our best unless we tackle them

More difficult to deal with are certain fundamental psychological trends which are frequently found in skin cases. Miller (1944) who worked for a short time at Ragley Hall showed that many of the patients there had a self-centred narcissistic character Patients with pompholyx and hyperidrosis have often a chronic anxiety state whilst those with lichenified lesions may show obsessional features. We must try to re-educate these people and guide them into a better attitude towards life. Individual analysis is obviously impossible, except in rare cases, but a lot can be done by group psychotherapy both overt in the form of talks and group occupations and, less obviously in the general atmosphere of the institution in which these patients are being treated

The Ragley Hall experiment

A serious attempt at organizing such rehabilitation was made by the Army in 1943 The loss of man-power from skin conditions was causing concern, and large numbers of men were spending the bulk of their time in hospital or else were being invalided out of the Army An auxiliary hospital (B R. C. S. and O St. J) of 75 beds was set aside as a long-term convalescent centre where skin cases could be rehabilitated. The site chosen was a fine English mansion, standing in its own park in lovely country It had an enthusiastic staff consisting of a matron, two trained sisters and numerous V.A.D.s, an occupational therapist and an administrative sergeant the Commandant was the very sympathetic owner of the house. The first object was to create an atmosphere very different from that in a military hospital, where most of these men had already spent so many months and in which they had lost faith. Discipline was different, routine military restrictions were relaxed, but on the other hand the men could no longer spend their days smoking round the stove. The impersonal attitude of most military hospitals was replaced by the interest taken in each individual by the staff, and the men were encouraged to unburden themselves by discussing their problems with Matron or one of the others. Unfortunately we had no psychiatrist available, except for a short period when Major E. Miller was studying a sample of our patients, but one was soon driven to the conclusion that a psychiatrist would have been more useful even than the visiting dermatologist.

Each man had to carry out a programme of 5 hours work a day This consisted of domestic work, gardening, carpentry various types of farm work, physical training, and a limited amount of munition work. This latter was difficult to provide in a rural district, but some simple tasks which did not require any previous training were found, though they were unfortunately of an uninteresting repetitive type. The object behind this latter work was to give an opportunity to these men to contribute something to the war effort, to think of their country and not of themselves, and to regain a little of their self-esteem after months and even years of futile idleness. During the summer harvest and other farm work replaced the munition work, and was more popular

Although a daily minimum of 5 hours work was laid down, many men did more, especially in the wood workshops. Everyone had to do physical training unless expressly forbidden by the dermatologist, though it was modified for those with bad feet. Thus many men who declared that sweating brought out their rash soon found themselves doing strenuous physical training with impunity One might note here that modern army physical training is much more varied and interesting than the old-fashioned Swedish drill. In the evenings there was plenty to occupy the men s time with lectures, concerts, whist drives, dances, etc. Much of this social activity was got up by the men themselves and was run by the men s own entertainment committee. Discipline was at times a little difficult with 75 fit soldiers, but very soon Ragley Hall became so popular that the threat of being sent back to a military hospital usually brought the offenders to heel.

The results were very interesting to watch. In almost every patient there was a marked improvement, both in the skin and in the morale, soon after arrival. This,

of course, is a well-known phenomenon when a skin patient is put on a new treatment, but our object was to make this change permanent by gradually increasing the man's activities and giving him confidence in the possibility of recovery. The man's self respect was increased in other ways: thus a depressed young soldier with seborrhoea, whose face had been painted with gentian violet for months, was found by Matron soon after his arrival in his own room during a dance, unwilling to take part. She persuaded him to join the others and shortly afterwards one of the prettiest V.A.D.'s asked him to dance, much to his amazement, for as he afterwards told matron "fancy a girl like that wanting to dance with someone with a face like mine". From that day he became an ardent dancer and his morale never looked back. Many patients were discharged from hospital in this phase but a certain proportion seemed to realize after a time that it was pleasanter to rehabilitate at Ragley Hall than to return to army life, and so they clung to Ragley's protective atmosphere and tended to relapse at the first indication of discharge. This tendency is of course more marked in the rehabilitation of soldiers than civilians, for the latter have a stronger motive for getting better as they will be returning home and are probably suffering financial loss whilst being off work. Nevertheless, in any form of rehabilitation this weaning process of men who have come to rely on the staff of the rehabilitation centre may cause some difficulty.

The importance of incentive was shown by a sudden enthusiasm for farm work which occurred during the first summer: men who had previously complained that they could not stand up to physical training suddenly found they could manage a whole day's harvesting. I wish this could have been attributed to an altruistic desire to "do their bit" for their country but actually it was because the men were unofficially getting pocket money from the farmers.

The final disposal of men was facilitated by the army system of categorization which enabled one to label a man so that he would only be given work within his capacity. Later in the war this was amplified by the Army Selection Centres, where the Selection Officer aided by a medical report, gave personal attention to each categoried man, so that he was directed into the type of work which he wanted to do and which was compatible with his physical state.

Some 800 men passed through Ragley Hall in its first two years (Bolam, 1945), and their average length of stay was 8½ weeks: of these 584 returned to duty and 216 were discharged from the services. A follow-up of a group of the former some months after discharge showed that 75 per cent were at full duty and a further 17 per cent on light duty. These results are encouraging when it is realized that these men had spent on an average two-thirds of their total army service passing from hospital to hospital. The number (216) who were discharged from the service consisted chiefly of men who were really unsuitable for rehabilitation.

It was only gradually as we gained experience, that we were able to issue instructions indicating which types of skin conditions were likely to benefit from rehabilitation: thus a large number of cases of khaki dermatitis, many with positive patch tests, reached Ragley Hall and almost all of these had ultimately to be discharged. It was also found that some hospitals tried to use Ragley Hall as a means of getting rid of their difficult cases, and this dumping is a danger which would have to be guarded against in a similar venture in civil life.

The conditions which, on the whole, responded well to rehabilitation were (1) seborrhoeic dermatitis of moderate severity (2) eczema of the same degree (3) impetigo of chronic or relapsing type (4) persistent or relapsing pyoderma, so common in the Army e.g. ecthyma, boils, folliculitis, etc. (5) sulphonamide dermatitis, which so often relapses if the man is exposed too soon to non-specific irritants such as sun, winds, or rough clothing (6) lichen planus. On the other hand, as already mentioned, khaki dermatitis responded badly: really severe and chronic constitutional eczema and seborrhoeic dermatitis usually failed to clear permanently also sycosis barbae. Psoriasis often improved at first, but relapsed when the effect of the new surroundings had worn off.

THE FUTURE OF REHABILITATION IN CIVIL LIFE

Ragley Hall was an expensive experiment which justified itself in wartime when saving of man-power was all-important. In civil life money spent on such an institution is not justified until the ordinary in-patient hospital treatment of all skin conditions is adequately catered for. An enormous amount of harm is done, particularly in cases of industrial dermatitis, by letting a patient drag on under inexpert treatment, himself clumsily and irregularly applying inadequate quantities of an unsuitable ointment. A skin patient always gets better more quickly in hospital, and the earlier he is admitted, the shorter is his stay. A man should not be allowed to learn that skin conditions are chronic. Ideally he should never stop work, but be moved at the first sign of trouble to some other job: this is rarely done for many reasons. It means regular medical supervision in the factory: frequently it is impossible in a small factory to find a suitable alternative job or the employer does not make the effort to provide such work. Under the present method of insurance, the employer takes the easier line of stopping the man entirely and letting him draw compensation, instead of searching the factory for some job which the man could do, even though it might mean paying him temporarily a higher wage than the work was worth. If the employer co-operated in this way everyone would gain in the end: the man would not experience the anxieties and distress of being off work, and his skin would be rehabilitated whilst at the temporary non-irritating work. The employer would benefit by a lowering of his insurance premiums, whilst the country would gain by having a man partly employed instead of wholly idle. Unfortunately another factor working against such a solution is the lack of liaison between the factory and the man's private doctor: thus the latter on seeing a man with dermatitis, usually tells him to stop work instead of co-operating with the works' doctor, assuming there is one, in finding him a suitable job.

When a man has to stop work, all the resources of dermatological therapy must be brought to bear on him at once in order to get him better. It is these early weeks, during which the man anticipates a speedy return to work, that count. He must not be allowed to drift with consequent loss of morale: he must not be allowed to accumulate anxiety over the settlement of his compensation and his future security: he must be made to realize that everyone, from the doctor to the employer, is doing his best for him.

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For those who are permanently partly incapacitated, the Disabled Persons (Employment) Act, 1944 is of assistance, and can be applied to patients with skin diseases just as much as to those with other maladies. To instrument its provisions there should be available an accurate analysis of all the possible jobs in the area, so that the patient could be promptly directed to the right place by the Disablement Rehabilitation Officer. The knowledge gained from this would be of great value in providing temporary employment for patients requiring rehabilitation, assuming that the scheme outlined above for grouping small firms together could be put into force.

The psychological aspect of treatment is implicit in most of the above suggestions, in fact they are aimed at preventing the development of any psychological problem at all. In the straightforward case of a man's resistance to some definite irritant breaking down, if he is handled along the above lines no such difficulties should arise. Problems will arise, however, in two ways: first there is the man who has not been handled in this way and has been allowed to become a chronic case with fears about his future and bitterness towards his employer. Such a man must be re-educated to a reasonable attitude. He must be given and feel that he is getting proper treatment, if possible in hospital away from his home environment, which is probably depressing and pessimistic. Then he must be interviewed sympathetically, his grievances discussed and assurance given about his future. This does not require a psychiatrist, but can be done by the dermatologist himself if he has time, or by a sympathetic trained social worker. The restoration of a sense of security for such a man is not easy but the Disabled Persons (Employment) Act should help in the future.

A more difficult problem is the patient who has some deep-seated psychological tendency which is having a bad effect on his skin. A typical example of such is the highly strung, tremulous, anxious type of patient with gross hyperidrosis and recurrent pompholyx. Any extra worry or strain, the fear of reprimand or thought of promotion may precipitate an attack and, once he is off work, the worry of this adversely affects his skin. Here it is not a matter of modifying a temporary attitude, but of changing a man's whole character and teaching him to adapt himself to a mode of life within his capabilities. It is here that the trained psychiatrist is necessary and so, possibly, is a period in an establishment for psychological rehabilitation.

Summary

Summing up the problem of rehabilitation *in civil life* one can say that rehabilitation should be an aspect of treatment from the moment a man develops skin trouble and not a means of rescuing him from a state of unnecessary invalidism into which he has been allowed to drift. Every man developing skin trouble should be given the best treatment possible as soon as possible: this in itself would help greatly to restore his morale, in addition to preventing the production of many chronic cases. Even under present circumstances, much more could be done in hospital in the way of diversional therapy to maintain morale, and of simple physiotherapy to keep up the general physical condition of the patient.

If possible he should be admitted to hospital failing this he must have expert daily dressing, at the factory or as a hospital out patient, or by the district nurse Adjuvant treatment such as x ray irradiation should be employed at the first possible moment. A sense of urgency must be imparted to all who are looking after him. Efforts must be made to fill in his time and prevent boredom and introspection It is hard to provide suitable occupation for out patients, but encouragement and advice can be given by the lady almoner to each man on how best to occupy his enforced idleness and if possible how to find something useful to do. In hospital, the full range of diversional therapy such as rug-making, work with perspex etc should be brought to bear on him. The introduction of a competitive element into such work adds a great incentive Specific occupational therapy is rarely available in an ordinary hospital but the man can at least be sent to the physiotherapy department, where he can do suitable exercises and take part in group physical training, and thus maintain his general physical condition and add to his mental alertness. The effect of this on a man who has settled down in bed to a comfortable invalidism is sometimes remarkable.

On discharge from hospital the man is usually not fit to return at once to full work and it is here that further rehabilitation would be of service. The best method is to recondition the man in his own work place In big firms this can be done by putting the man on suitable light work until he is ready to resume his old job or if necessary some other appropriate work. The works medical officer should have an accurate knowledge of all the processes in the factory and sufficient executive authority to be able to direct a man to such work. Some firms have a special department to which all employees are sent after being off sick for any considerable period and where they perform carefully selected work under the supervision of a trained and sympathetic foreman In small firms or those which only perform a limited number of processes or handle one noxious agent throughout, such arrangements are not feasible, even when the management is willing to help For these there are two possible solutions A rehabilitation centre on the lines of Ragley Hall might be provided with a wide range of occupations so that the man could harden himself off in his own appropriate trade and regain his self-confidence. It would, however be unwise to segregate skin patients in a centre by themselves, as at any time they tend to develop the leper complex and such isolation would aggravate it. They should undergo rehabilitation with other types of patient, though of course, their progress would be supervised by someone with a knowledge of skin conditions. The average time spent in such a centre would be less than that spent by soldiers at Ragley Hall because civilian workers would have a greater incentive to return to work. An alternative solution would be to group a number of firms together so that a man could be moved to a firm where suitable work was available. Under present legislation employers are naturally unwilling to take on a man who has just recovered from dermatitis for fear of becoming liable themselves in the event of a further breakdown Possibly there may be a change of attitude when the new Insurance Act is in force. Trade union restrictions also make it difficult for a man to change his job even temporarily in his own factory and it would often be to the workman s benefit if their rules were more flexible.

CHAPTER 18

ON THE USE OF STATISTICS

E. S. Cooper Willis

In this chapter it would be out of place to attempt to provide a few rules of thumb for carrying out elementary statistical tests. It will be more useful to state in general and non-mathematical terms what the duties of a statistician are, so that, when a problem involving statistics arises, the clinician may have some idea of the assistance which he may obtain from consultation with a specialist in this branch of mathematics. A second function will be to give a general and logical explanation of the statistical outlook—which is really the scientific outlook—and to show that its base is refined common sense, rather than some fearful magic.

THE NATURE OF MATHEMATICAL STATISTICS

Mathematical statistics consist in essence in the manipulation of numerical data in order to make comparisons and draw conclusions. The most satisfactory investigations are those which are so designed that only the most elementary manipulation is necessary to make the results tell their story Thus, if we wished to know whether chilblains were more common among Englishmen than English women, we might proceed—had we the patience and resources—by examining every English person in the world, and so obtain a definite answer to our question but such an immense labour would be quite unnecessary for statistical treatments have been devised to enable this type of question to be answered more economically and rapidly albeit with a certain sacrifice of precision. It may be noted here that, even if every English person was interviewed, the research might not be satisfactory for while there would be no doubt about the answer at the time that the data was collected, nevertheless we should not know unless we employed statistical methods to evaluate our data, whether it was safe to assume from the results that the chilblain incidence in, say the next generation would be the same (provided, of course, that there had been no change in extrinsic and intrinsic factors). Suppose our results had been as given in Table I

TABLE I. CHILBLAIN INCIDENCE

	Males	Incidence	Females	Incidence
With chilblains Without chilblains	7,999,980 12,000,020	39 9999 per cent	10,000,000 15,000,000	40 per cent.
Totals	20,000,000		25,000,000	

Ideally on discharge from hospital a man should be rehabilitated on suitable work at his old firm failing this, such work should be found in some associated firm or in a rehabilitation centre. Efforts should be made to relieve the man of worry about the future, so that he will no longer have any need to cling to his compensation for security Where, however there is gross psychological instability reacting adversely on the skin therapy and rehabilitation along definite psychiatric lines must be employed

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experiment these terms may be very precise. Thus, in a large-scale trial of a certain new drug, the writer was able to state not only that the use of this new drug resulted in a significantly shorter stay in hospital for those treated with it, compared with patients given a control treatment, but also that the chances were less than 1 : 100 that the shortening of stay in hospital produced by the new treatment was less than ½ day or more than 2½ days. (*Vide* MacKenna and Cooper Willis, 1945.)

The statistical approach

From these examples a number of the most important facts concerning the statistical approach can be stated.

(1) *Numerical difference and statistical significance.*—Firstly, no numerical difference can be accepted without questioning its statistical significance—that is without carrying out the necessary tests to discover how likely it is that such a difference could have arisen by chance alone: once this probability is known, the results are set in their proper perspective. The actual level of improbability which can be accepted as making a result significant is a matter of choice, though odds of 1 : 20 and 1 : 100 are usually taken as marking the levels of possible and probable significance. In practice, however, whatever the value of the probability that a given result is not due to chance, we cannot accept that result as being more than suggestive if it is based on a single small experiment, for the methods by which the values of chance are calculated depend upon the use of models, which are not necessarily applicable to the world of reality. Thus the toss of coins, the turn of cards, or the results of drawing coloured billiard balls at random from an infinitely large hat, can give some idea of purely chance effects: but in the real world, and particularly in Medicine, there are a host of influences, individual idiosyncrasies, reactions and interactions on the part of patients, nurses, and doctors, as well as innumerable differences in interpretation, which, whilst they constitute part of the true error to which an experiment is subject, do not necessarily behave in the simple manner expected of coins, cards, or balls. Therefore, the prudent course is to regard results obtained in a single hospital or by one or two clinicians—however significant statistically—as only being suggestive and not proved until they are confirmed by large-scale trials or by the accumulated data of widespread experience.

(2) *Size of sample and accuracy of conclusions.*—The second point of importance is that the larger the number of cases on which a statistical conclusion is based, the more accurate is that conclusion likely to be. In mathematical terms, the precision of the information increases with the square root of the numbers in the sample. The smaller any difference is, the larger the number of cases required to substantiate it.

Table II shows the way in which the chance errors of an experimental statistic decrease as the size of the sample increases.

Taking as a basis the precision with which an average, such as the average height of the general population, can be determined from a random sample of 10 individuals, Table II gives the reduction in error as the sample is increased from 10 to 1,000 cases.

The difference in incidence between the two sexes is 0·0001 per cent or 1 per million should any importance be attached to this? The answer of course, is No for in the biological sciences and in Medicine the factor of chance is usually encountered, and small differences can never be accepted at their face value until they have been critically examined to determine whether or not they have arisen because of the innate variability of living organisms.

Statistical significance

Such examination is one of the main tasks of the statistician He makes comparisons and then checks the magnitude of the resulting differences against a mathematical model named chance In practice he refers his results to tables showing how often a given occurrence might be expected to happen in circumstances in which random factors alone operated and from this comparison he can give some estimate of the confidence which any conclusion deserves

Suppose, for instance, that long experience has established that normally 50 per cent of patients recover from a disease, but that a new treatment administered to a sample of 10 patients who have been selected at random has cured 8 of them Does this result indicate that the new treatment is superior to older therapies? To test the matter we can calculate how often chance would produce 8 or more recoveries in a sample of 10 if the recovery rate were really 50 per cent

This problem is similar to inquiring how often tossing 10 coins together would result in 8 or more of them coming to rest with the same side uppermost. We find that in 100 throws this should happen by pure chance in about 10·9 per cent of the trials From this analogy we can infer that the data on the new treatment are not sufficient to warrant any great confidence in the superiority of the new method over older treatments. If the sample of patients had been twice as large, and if the ratio of those who recovered to those who were not benefited or were made worse had been the same the probability of chance producing this recovery rate would have been only about 1 5 per cent therefore the result would be more suggestive of a real difference between the new treatment and the older regimens. Had a second trial been made, so that there were 2 sets of 10 results, each giving the same proportion of successes, the *statistical significance*—as it is called—of the difference between the new and old treatments would have been further enhanced and the probability that the experimental results had arisen by chance would have fallen to about 0·5 per cent

That this third probability is lower than the second indicates that by a suitable design the precision of an experiment can be improved—in this case because the investigator is enabled to examine more fully the internal consistency of his results. This point is discussed further below

In an experiment, once the significance of the results has been determined, we can go on to assess the likely distance from the truth of the various estimates derived from the experiment In the above example, 10 cases are insufficient to make it worth while attaching any particular importance to the actual recovery rate of 80 per cent, and it is only justifiable to say that the new treatment appears to be better than the older ones If more data are available one may be justified in stating one s conclusions in more definite terms and in a properly planned

many factors have to be considered. For example, consider what determines the speed at which a patient recovers from a disease besides the factor of treatment (which, perhaps, is the matter under investigation), allowances may have to be made for variations in the potency and type of the invading organisms, variations in the susceptibility of different patients and in their individual responses to treatment, variations in age, previous medical histories, lengths of infection prior to treatment, and so on the manner in which each patient is nursed and fed may make a considerable difference, and allowances may have to be made for a set of psychological factors such as the patients reactions to their disease and their environment further the personalities of doctors and nurses may have to be taken into account. All these things, and many more, make it very doubtful whether a simple experiment with a small sample can ever give very reliable results in medical investigations, for the difficulties of obtaining a truly representative set of conditions are so considerable. Hence the design of medical experiments is of great importance.

As an example of the manner in which design improves the efficiency of an experiment, I may quote the classical case given by Student (*vide* Pearson, 1931), as set out in Table III.

TABLE III. ADDITIONAL HOURS OF SLEEP GAINED BY THE USE OF TWO FORMS OF HYOSCINE HYDROBROMIDE

Patient	(1) *Dextro-rotary form*	(2) *Laevo-rotary form*	*Difference (2—1)*
1	0.7 hours	1.9 hours	+1 hours
2	−1.6	0.8	+ 4
3	−0.2	1.1	+1.3
4	−1.2	0.1	+1.3
5	−0.1	−0.1	−0.0
6	3.4	4.4	+1.0
7	3.7	5.5	+1.8
8	0.8	1.6	+0.8
9	0.0	4.6	+4.6
10	2.0	3.4	+1.4
Average	0.75 hours	2.33 hours	+1.58 hours

By considering the difference in results which the 2 forms of the drug had on the same patients, it is possible to show that the laevo-rotary form is significantly better than the dextro-rotary *for the probability that the effect was due to* chance alone is well under 1 100. Had the 2 forms been tried out (with the same results) on 2 separate samples of patients, thus making it impossible to eliminate the individual *reactions common to the 2 drugs*, the test would not have yielded a significant answer the chance probability being approximately 1 10. Although, of course, so small an experiment would require repetition to be quite convincing, the first design affords much more accurate information than does the second for the same amount of work.

TABLE II PRECISION AND SIZE OF SAMPLE

Number in sample	Error of the average
10	Taken as 100
40	Proportionately 50
90	" 33⅓
160	" 25
640	" 12½
1,000	" 10

Index of the dispersion of the averages calculated from each sample around the true average.

It is evident that if the size of the sample has to be increased a hundredfold to obtain a tenfold increase in precision it becomes a somewhat expensive and laborious business to obtain a high degree of reliability from an increase in sample size alone.

(3) *Reliability and design* —The third point is that increased reliability of results can be obtained not only from an increase in the sample size but by suitable design of the experiment. Readers will have noted that, in our earlier example, 20 cases treated as a single experiment gave a less precise result than did 2 separate experiments each with 10 cases. This was because the second plan provided extra information as to where in the proceedings the failures of the treatment occurred.

In both cases 4 patients out of 20 did not benefit by the treatment but in the first case all that we knew was that there were 4 out of 20 patients who did not benefit In the second case we knew that there were 2 failures in the first set of 10 patients and 2 in the second Reverting to our coin analogy let us call failures of the treatment heads and successes tails We now need to compare the respective chances of obtaining 4 heads out of a toss of 20 coins, and of obtaining 2 heads out of 10 coins in 2 successive tosses of 10 coins.

If 20 coins are tossed one after another and we confine our attention to the occasions on which 4 heads occur we shall find that these 4 heads can be distributed between the first and second sets of 10 coins in 5 ways (i.e. with 0 in the first, and 4 heads in the second set of 10, and so on with 1 2, 3 and 4 heads in the first 10 coins)

In our second experimental design we know which of these 5 possibilities occurred and its single-chance probability is naturally less than that of the aggregate of all five. This second and greater chance probability is the one appropriate to the result of the first experiment.

The precision of an experiment may be increased, first, by making a more intensive study of the given number of cases so that conclusions may be drawn from the internal consistency of the data, and secondly by making arrangements so that the interference caused by external and irrelevant factors is reduced to a minimum In Medicine, the design of experiments is frequently difficult, for so

many factors have to be considered. For example consider what determines the speed at which a patient recovers from a disease: besides the factor of treatment (which, perhaps, is the matter under investigation), allowances may have to be made for variations in the potency and type of the invading organisms, variations in the susceptibility of different patients and in their individual responses to treatment, variations in age, previous medical histories, lengths of infection prior to treatment, and so on: the manner in which each patient is nursed and fed may make a considerable difference, and allowances may have to be made for a set of psychological factors such as the patients' reactions to their disease and their environment: further the personalities of doctors and nurses may have to be taken into account. All these things, and many more, make it very doubtful whether a simple experiment with a small sample can ever give very reliable results in medical investigations, for the difficulties of obtaining a truly representative set of conditions are so considerable. Hence the design of medical experiments is of great importance.

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3	−0·2	1·1	+1·3
4	−1·2	0·1	+1·3
5	−0·1	−0·1	−0·0 "
6	3·4	4·4	+1·0
7	3·7	5·5	+1·8
8	0·8	1·6	+0·8
9	0·0	4·6 "	+4·6
10	2·0	3·4	+1·4 "
Average	0·75 hours	2·33 hours	+1·58 hours

By considering the difference in results which the 2 forms of the drug had on the same patients, it is possible to show that the laevo-rotary form is significantly better than the dextro-rotary for the probability that the effect was due to chance alone is well under 1 in 100. Had the 2 forms been tried out (with the same results) on 2 separate samples of patients, thus making it impossible to eliminate the individual reactions common to the 2 drugs, the test would not have yielded a significant answer: the chance probability being approximately 1 in 10. Although of course, so small an experiment would require repetition to be quite convincing, the first design affords much more accurate information than does the second for the same amount of work.

TABLE II PRECISION AND SIZE OF SAMPLE

Number in sample	Error* of the average	
10	Taken as 100	
40	Proportionately	50
90	"	33⅓
160	"	25
640	"	12½
1,000	"	10

* Index of the dispersion of the averages calculated from each sample around the true average.

It is evident that if the size of the sample has to be increased a hundredfold to obtain a tenfold increase in precision it becomes a somewhat expensive and laborious business to obtain a high degree of reliability from an increase in sample size alone.

(3) *Reliability and design* —The third point is that increased reliability of results can be obtained not only from an increase in the sample size but by suitable design of the experiment Readers will have noted that in our earlier example 20 cases treated as a single experiment gave a less precise result than did 2 separate experiments each with 10 cases This was because the second plan provided extra information as to where in the proceedings the failures of the treatment occurred

In both cases 4 patients out of 20 did not benefit by the treatment but in the first case all that we knew was that there were 4 out of 20 patients who did not benefit. In the second case we knew that there were 2 failures in the first set of 10 patients and 2 in the second. Reverting to our coin analogy let us call failures of the treatment heads and successes tails We now need to compare the respective chances of obtaining 4 heads out of a toss of 20 coins, and of obtaining 2 heads out of 10 coins in 2 successive tosses of 10 coins.

If 20 coins are tossed one after another and we confine our attention to the occasions on which 4 heads occur we shall find that these 4 heads can be distributed between the first and second sets of 10 coins in 5 ways (i e. with 0 in the first, and 4 heads in the second set of 10 and so on with 1 2, 3 and 4 heads in the first 10 coins)

In our second experimental design we know which of these 5 possibilities occurred and its single-chance probability is naturally less than that of the aggregate of all five This second and greater chance probability is the one appropriate to the result of the first experiment.

The precision of an experiment may be increased first by making a more intensive study of the given number of cases so that conclusions may be drawn from the internal consistency of the data and secondly by making arrangements so that the interference caused by external and irrelevant factors is reduced to a minimum. In Medicine, the design of experiments is frequently difficult, for so

making small preliminary trials and then, by using the experience so gained, framing large-scale experiments. All that can be said quantitatively with regard to the number of cases to be investigated, is that few investigations require more than 2,000–3,000 cases, and that little of value can be inferred from fewer than 10–20 cases. Obviously however the sample size depends upon the nature of the effects to be studied. If a disease has a death rate of 100 per cent and 10 patients treated with a new antibiotic recover then an important discovery has been made. On the other hand, an investigation concerning small differences in rates of cure may well need a few thousand cases.

It is not always possible to formulate an exact question at the commencement of a research. Indeed, much material is collected without a definite research object. The case records of a specialist, accumulated over a period of years, could provide data of inestimable value, but often they are valueless because they are not uniformly compiled. In planning case notes, the clinician should decide never to omit certain basic data, which (so far as is possible) should be given in numerical form. He should endeavour to have consistent criteria of success and failure, which are applicable to each case and which are always incorporated in the notes. *The best method of recording such matters is discussed later (p. 404).*

STAGE II.—THE DESIGN OF THE INVESTIGATION

After the experiment has been planned, the next stage is to design an experiment which will provide the answers in the most economical and satisfactory manner. It is at this stage that a statistician should be consulted (if his opinion has not already been sought), for if his assistance is requested only at the termination of the investigation he can often do little except state that the results are valueless owing to faulty design of the work, or—for the same reason—have been wastefully and expensively garnered.

Treatment of disturbing factors

There is no great mystery about the principles of experimental design. Much of the work consists in sub-classifying the data so as to eliminate various factors likely to have a disturbing effect on the results, and thus preventing them from increasing the random variation or "errors" of the experiment.

This can be done in two ways: either by direct elimination of the source of error or, if that is not possible, by framing the investigation so that the error can be removed statistically. For example, suppose that we wish to test the effect of two drugs, Benzedrine (amphetamine) and Sodium Amytal, on persons carrying out an intelligence test. Clearly the major part of the variation found in the resulting scores will be due to variation in the subjects' intelligence; therefore, we must attempt to eliminate this effect so as to obtain an economical experiment. If we had unlimited resources we could neglect to do this, and simply compare the average scores of 3 large random samples: the first untreated, the second after taking Benzedrine, the third after taking Sodium Amytal. However each sample would have to consist of at least several hundred individuals to ensure that the experimental differences were not due to the innate differences in intelligence of the

After this general introduction it will be profitable to consider in more detail the various stages through which a well planned statistical investigation should pass

STAGE I—PLANNING THE INVESTIGATION

This is the stage for exact definition and thought, for the first decision must be an accurate and quantitative formulation of the problem Thus supposing that we are interested in a new drug for the treatment of impetigo our vague and preliminary idea may be, How good is this drug? We have then to decide exactly what we mean by the question. This involves, first the adoption of a criterion of goodness and, secondly the adoption of some standard with which to compare the performance of the new drug. In many instances an adequate test of goodness would be a satisfactory response to treatment, so that the number of days from the first application of the drug to the final healing of the lesions was few As a standard or control we might adopt the result of treating impetiginous lesions with some other drug—perhaps one commonly used, or one which had been generally accepted as being the most satisfactory In some types of research the controls might be left untreated but such a course is usually repugnant to humanitarianism

Conditions of the experiment

As a result of our planning, the experiment should tell us whether the new drug produces a cure more quickly than does the control but before we proceed further a good many definitions are necessary this may seem to be pedantic but experience has shown it to be all important For example what type of impetigo is to be used for the experiment? Is the investigation to be confined to children, or to adults? Are cases with lesions in the scalp to be included? What is meant by healing the first appearance of complete epithelialization or the return of the skin to its normal texture and appearance? When all these matters have been decided a plan has to be made as to the exact technique of application of the drug, and this schedule has to be rigidly adhered to one point for example are crusts to be removed at the commencement of therapy and during the course of treatment—or not?

We have next to consider all the factors which may have an influence on our work. Thus the type of skin involved the general health of the patients, their age and sex, and the general efficiency and reliability of the nursing in the hospital concerned all are matters which could affect our results. We must decide which are to be included in the research The larger the scale of the investigation, the larger is the number of the factors which it is worth while to take into account.

Size of the sample

The number of cases to be investigated must be decided in this respect, opportunity and the extent of our knowledge of the subject must be our guide In advanced research in new fields of investigation the inquirer has often to grope his way and after weeks of work, discard his results and return to this point and start planning again Therefore a new field is most economically explored by first

An example will make the design more clear. If we have 3 churns (1, 2, and 3), 3 treatments (A, B and C), and 3 repetitions on 3 separate days, the design recommended will be of the following type:

	1st day	2nd day	3rd day
Churn 1	A	C	B
	C	B	A
„ 3	B	A	C

The following designs might prove to be unsatisfactory

Churn	1st day	2nd day	3rd day		Churn	1st day	2nd day	3rd day
1	A	A	A		1	A	B	C
	B	B	B	or	2	A	B	C
3	C	C	C		3	A	B	C

In the first design the differences between the averages of the treatments, between those of the churns, and between those of the days, give the estimates of the separate effects of each for when the sum of the three A's is to be compared with the three B's, the same churns enter into each sum, and so the difference between these two sums is not affected by differences between the churns. On the other hand, in the second design the average of the three A's will be based on different churns from that of the three B's and hence two effects are confounded together The principle involved is that if it is desired to remove a disturbing effect and measure its size, it must be equally represented on each side of whatever comparisons are made. Thus, if men and women have different reactions to two treatments which we wish to compare, we take equal groups of men and women and subject both groups to each treatment. In this way we obtain a comparison between the treatments which is not affected by sexual differences, and vice versa.

In designing an experiment it is prudent so to arrange matters that the various factors which might influence the final results can be kept separate, whether or not they are actually expected to influence it, for it is preferable to take a little unnecessary trouble in the statistical lay-out than to hazard the value of the whole experiment.

Need for controls

Essentially the conclusions from many experiments are comparisons. Generally speaking, a single absolute value is of little interest only when this value is seen in its proper position relatively to other values can it assume full significance. Thus, to know that 16 per cent of a sample of sufferers from pediculosis capitis got less than 10 marks (out of a possible maximum of 100) in an intelligence test is of little importance, until we discover what percentage of a random sample of the ordinary population would usually get similar low marks. If we knew that only 5 per cent of a representative sample of the population obtained as low a score, and if the numbers in the samples were sufficient to make the difference statistically reliable, we should have some evidence for supposing that the presence of head lice was associated with low intelligence. Similarly if we test a preventive treatment for chilblains before the winter and find that, as a result, 5 per cent of those treated fail to suffer from chilblains that winter we cannot make any conclusion concerning the efficacy of the preventive measure without knowing what will happen to an

persons in the 3 samples Large numbers would also be needed in this design before the experimental errors could be reduced to a sufficiently low level for the differences due to the effects of the drugs to become statistically significant.

(1) *Elimination of factors*

Now one of the objects of experimental design is to obtain reliable results by the use of relatively smaller samples, so we must consider how we can plan the investigation to fulfil this requirement. What other courses are open to us? We could test everyone who was available with a preliminary and different intelligence test, and select for further testing only those whose results fell within certain narrow limits thus a nucleus of homogeneous material could be obtained. Alternatively we could eliminate the factor of varying intelligence by statistical means, simply by recording the undrugged scores in the preliminary test and by working with the difference between each individual's two test scores, in a manner similar to the hyoscine experiment shown in Table III. Age and other quantitative variables could also be eliminated statistically provided that they were recorded for each case.

(2) *Separation of factors*

In practice, it is often difficult exactly to measure in advance the sources of error although they may be common to a group of cases.

Thus, in trials concerning the efficiency of one of the sulphonamides when used for the treatment of impetigo it was found that whatever treatment was employed, each hospital had a significantly different average duration of stay for in-patients suffering from this malady To eliminate error due to this factor it was necessary for each hospital to treat a series of cases with the sulphonamide and another series with the control remedies, and not to take the obvious course of allowing one group of hospitals to test the sulphonamide and another group to furnish the controls. By taking the former course the statistician could work with the set of mean differences obtained between the treatments in each hospital the differences being free from any general bias due to variations in efficiency in the hospitals concerned.

The writer was once asked to analyse an experiment on the results of different methods of sterilizing milk churns. Faulty design had made the results useless. Each of 6 sets of 2 churns had been kept to a single different treatment throughout the experiment which consisted of a number of repetitions of the treatments on successive days. However it was found that 2 churns treated alike often gave significantly different average bacterial counts, and it was evident that there was a high probability of the different churns having specific influences on the results. Further trials showed that some churns were easily sterilized whilst others always gave high bacterial counts. The original design of the experiment gave no way of separating the influence of the churns from that of the treatments and so could not provide reliable data on the questions which it was planned to answer A further complicating factor was that the data indicated that climatic conditions on the day of the experiment influenced the results The subsequent experiments were arranged so that every churn had every treatment in turn and every treatment was given each day

about 1·4 times that of the estimate obtainable from the full set of 7 combinations (1·4 is the square root of 2). Usually it is not obvious to those unacquainted with the logic of statistics that an increase in the number of factors does not necessitate an increase in the total number of cases investigated, provided that the experiment is designed symmetrically as we have suggested.

The random sample

Having decided on the logical structure of our investigation, we have still another set of problems to consider these concern the securing of a random sample. The theory of statistics, as well as common sense, requires that the cases shall be chosen in such a manner that bias does not enter into their selection.

Definition of a random sample.—For a sample to be random every individual in the population sampled must have an equal chance of selection, and the selection of any individual must leave unaffected the chance of selection of any of the remaining individuals.

Equal chance of selection.—A sample obtained by taking the first 100 people whom one met in Piccadilly would certainly be most unrepresentative of the people of England, since those who frequent London would have a much greater chance of selection than those who live far from the Metropolis. The sample might also be unrepresentative of the population of London, for if the sample was chosen in the day-time it would be biased against those whose work kept them indoors at that time it might tend to exclude school-children, indoor workers, the very young and the very old. Moreover the people found in Piccadilly are probably not representative of those who may be found even in the streets of London as a whole, visitors, the well-to-do, and so on, being over-represented.

Independent selection.—The second point is that each member of the sample should be selected independently of the others. Let us suppose that, in order to ascertain their views on some political topic, we carefully choose a random sample of men, visit their homes, put our questions and then, in order to obtain the views of a sample of women, ask their wives, mothers, sisters and other women in their houses the same questions. The sample as a whole would tend to give a biased view of the opinions of the population, both because women living on their own would have no chance of inclusion and because the views of the women would probably be influenced by the opinions of their menfolk, or vice versa, and thus, instead of obtaining two or more different opinions in each household, only one would often have been obtained. Distortion due to such mutual influences can be avoided only if every person is chosen independently for otherwise there is always the risk that group influences of one sort or another may reduce the representative nature of the sample. In human affairs such influences as those of the family trade or occupation, the social class, the part of the country and the race, on the behaviour and sentiment of the persons concerned are of particular importance and every precaution against bias from those causes must be taken in sampling.

Randomness

The theoretical concept of randomness is a somewhat difficult one it may be understood as the absence of arrangement, which prevents systematic prediction

untreated but otherwise comparable group, and also perhaps, how similar groups fared under other methods In short it is vitally necessary to ensure that adequate controls exist.

Combination of factors

So far we have dealt with treatment as though it were a matter in which only one factor was involved Normally it consists of a set of different therapeutic measures, and we may require to test the efficacy of a number of factors together Thus, to revert to the matter of chilblains, we might be interested in deciding whether it was beneficial to keep these lesions covered and protected, or to apply an ointment to them or to administer vitamin tablets or calcium. In a case like this we can obtain the maximal amount of information by trying out every possible combination of therapy Thus we might arrange for 8 groups of cases to be observed

(1) A group in which the individuals were untreated
(2) A group in which the lesions were only kept covered
(3) A group in which the lesions were treated only with ointment
(4) A group *receiving internal therapy only*
(5) A group treated simultaneously like groups 2 and 3
(6) A group treated simultaneously like groups 2 and 4
(7) A group treated simultaneously like groups 3 and 4
(8) A group treated simultaneously like groups 2, 3 and 4

From such an experiment we could obtain not only the differences in efficiency of the factors singly but also their effects in combination.

An interesting point about such an experiment which is quite symmetrical is that each single comparison is as statistically reliable as if the whole investigation had been devoted to its elucidation although but one-quarter of the total number of persons available for the experiment at first sight seem to be relevant to it This is because the symmetrical nature of the design enables us to use 4 treatments on each side of any comparison and ascribe the difference to some single factor Thus, calling our factors A B and C and the controls O we have for the difference between the presence of the ointment (B) and its absence (O) the expression

$$\text{Difference} = \frac{(B+BA+BC+ABC)}{(\text{groups } 3+5+7+8)} - \frac{(O+C+A+AC)}{(\text{groups } 1+2+4+6)}$$

The difference between the two halves is due to the effects of B

It is not always possible to test every possible combination of factors in Medicine, for some factors might be deleterious to the patients but when the effects of several factors have to be studied, it is well worth considering the use of a complete set of combinations rather than some only as the amount of information obtained by the investigation may be thereby considerably increased. Thus, if the experiment concerning chilblains had comprised only 4 treatments but the same number of cases namely the controls (O) and 3 factors A B and C the difference between the effect of the ointment (B) and the untreated controls (O) is given by the comparison B–O which involves only half the data and so as the number of cases is the same as in the above example, may be subject to an *error*

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morbidity None the less, such a hospital could carry out trials of different treatments for a disease and obtain useful data. The patients suffering from this disease who presented themselves at the hospital would only have to be allocated at random to the treatments. This could be done by determining in advance an order of allocation e.g. case 1 to treatment A case 2 to treatment B case 3 to treatment C case 4 to treatment A, and so on. If this order was not decided in advance there would be a risk of bias, because the most serious cases might tend to receive either the most trusted or the least trusted therapy depending upon whether motives of humanity or desire to prove one treatment to be the best prevailed, unconsciously in the mind of whoever decided on the allocation of treatments.

Nevertheless, data based on such unrepresentative samples can never safely be taken as applying generally Thus the experience of the specialist with his private patients, whom one might normally expect to be of the wealthy and better nourished class, might well differ from that obtained in the public wards of a hospital situated in a depressed area. Again the results of treating children or young patients are often very different from those obtained when treating elderly patients Hence an experiment based on samples which are representative only of a restricted part of the population requires extension to other parts of that population before conclusions of general validity can be framed The neglect of this fact, that results obtained from a sample only apply strictly to the part of the population which that sample represents, has sometimes led to confusion and apparent inconsistencies in experimental results.

Selection of a truly random sample.—Let us now consider the selection of a truly random sample. In medical work the problem is likely to relate to a universe of patients or of documents. We may start with a universe of documents, for many problems can arise in sampling from hospital records. The method will depend upon the arrangement and the number of documents. If there were not more than 10 000 case records a random number could be allotted to each, and then only records the number of which ended with, say 9 would be selected In this way a random sample of one-tenth of the total could be drawn. Similarly other characteristics of the random numbers, or combinations of them, could be used to draw a larger or smaller sample. If the records already had a serial number of some sort on them there would be no need to allot a random number instead, a table of random numbers could be used to decide which serial numbers should be extracted.

Selection of more or less random samples.—If the number of case records was very great, the use of a table of random numbers might be too lengthy a business, and one might then select the documents from only one or two areas in the file. This would be possible if the filing were in alphabetical order although some index letters, such as M and O may contain a national bias (Scots and Irish respectively), and others, like S and W contain very common names which probably should be avoided. The writer's experience has been that samples selected from several index letters, such as F or N, can give satisfactory results with a considerable economy of labour and time.

In case of doubt, if the sub-samples from each single letter are kept separate, they can be tested for consistency with one another and, if they appear to form a

of the results of a process from succeeding more often than chance alone would allow

A random series of digits —Let us consider what is meant by a random series of digits. In such a series, if we were given the first 100 digits in the series, no matter how complex the mathematical formula which was used we could not predict correctly what the hundred-and first digit would be more often than once in 10 times, on the average. This percentage of success we should ascribe to pure chance, for out of 10 digits one must occur and therefore any formula or guess would tend to be right once in every 10 attempts. Now if the population can be *similarly* arranged at random that is, in no logical pattern or sequence, then it becomes simple to secure a random sample, for we can choose the first so many individuals up to the necessary total Thus we can select 10 cards at random from a pack by first thoroughly shuffling it to break up any systematic sequence in the cards, and then it does not matter whether we take the first or any other 10 cards. Similarly with a bag of differently coloured billiard balls we need only shake up the bag a fair number of times to obtain a random arrangement of the balls. With human beings the matter is more difficult, for they are arranged over the country *in a far from random pattern* little groups of one type or another tending to collect in definite places, and we cannot shake them all up or shuffle them. We find that the place where a person lives, as well as the social group to which he belongs, is usually determined by such factors as his wealth, profession etc. on the other hand a number of general influences are exercised by locality and the social group upon every characteristic of the individual

In order to secure a random sample from a population which is not, and can not be, conveniently arranged randomly we can make recourse to a model thus, if the numbers involved are not too large, we can put a numbered slip for each individual into a hat shake the hat and then select the necessary number of slips. More conveniently we could use a table of random numbers—that is numbers which are already known to be randomly arranged—and select our sample with the help of the table, as will be described later

Non-random samples —It may be asked why such attention and so much trouble should be paid to the randomness of a sample surely so long as obvious sources of bias are excluded, no more need be done? The answer is that only in the case of a truly random sample can we feel confident that every possible source of bias and disturbance has been excluded and that we have obtained a set of individuals who *are representative in every respect* within predictable limits of the population from which the set was chosen However it is true that for many purposes something short of a sample completely representative of the whole population concerned is sufficient and that for many purposes the labour involved in obtaining a truly random sample is so great that approximate methods must be used Moreover conclusions of limited application but none the less of considerable value can frequently be drawn from samples which are definitely not random. The patients of a single hospital are usually drawn mainly from the areas near to it, and therefore will probably differ in a variety of ways from those from other parts of the country their habits of diet and exercise as well as factors of climate, occupation and economic position, will affect their health and the typical pattern of their

a difference in fundamental definition between two sets of figures which appear at first sight to relate to the same thing. Particularly in Government departments, figures tend to be collected by different branches for different purposes consequently there are considerable variations in scope and meaning. Thus the Personnel and Medical sides of a Service department will often have several sets of quite different figures of (for example) the numbers of wounded. Even in smaller institutions there may often be differences in diagnosis length of stay in hospital and so on, which must be carefully noted. It is equally important to know the channels through which figures have passed Sometimes a multitude of sins lie hidden in some innocent-looking consolidated table. In a certain department, known to the writer during World War II, much confusion was caused by a very junior person who threw away all completed forms which looked to him improbable.

When information is to be specially obtained, the same sort of precautions must be observed, particularly when persons other than those who are familiar with the objects of the research have to record the data. Thus, only a few years ago, after all the materials had been collected, a large-scale research in a number of hospitals on the weight at birth and the subsequent growth of babies was entirely frustrated by a practice which was found to be usual in many of the hospitals. In order to lessen the mother's alarm at her baby's inevitable drop in weight in the first days of life, the nurses, unknown to their superiors, deducted a varying fraction of the total from the infants weight at birth.

Design of questionnaries and record sheets

Besides such difficulties there is the problem of designing record sheets or questionnaires so that they can be completed satisfactorily The aim must be to ensure that the information required is recorded with as little error as possible. Numerous errors arise from misunderstandings on the part of those questioned as to the real meanings of the questions, also from misunderstandings on the part of the investigators concerning the meanings of the answers, and finally from the difficulty of getting answers which are in the relevant form. For example, if a number of doctors have to record the duration of a hospital patient's illness, some will probably give the total stay in hospital, others a variety of different periods which conform to each doctor's idea of what is meant by duration of illness. An exact definition has to be provided, and the length of stay in hospital (except when another malady supervenes) will probably be the best period to choose, as it is, at least, not a matter of opinion. Here again, however one would have to say whether both, either or neither of the first and last days had to be counted. As an example of the second difficulty suppose, in a trial of several treatments, that there is a possibility of sulphonamide-sensitization occurring then, if the record sheet clearly asks whether or not it occurred, there can be no misunderstanding of what the doctor in charge of the case means. If however we merely ask for other relevant details some doctors may record all, or some, of the symptoms of sensitization without using the actual word sensitization and the investigator may be left in doubt whether or not to understand that sensitization occurred.

The third problem relates to getting a relevant answer The answers to such a question as Where do the lesions occur? may produce a variety of replies, some

homogeneous whole, the method is probably safe. If not, then a wider spread over the alphabet is necessary

When the question is one of selecting a sample of human beings, as in the survey carried out periodically for the Ministry of Health on the Nation's health the problem is more difficult. There is not a convenient list of the country's inhabitants, and therefore there is not an easy way of selecting a random sample scarcity of resources usually demands that such a sample be not too widely scattered over the countryside. In such a case it is customary to break down the main sample in advance into sub-groups, and to make the percentage of the whole number to be included in each sub-group equal to the proportion prevailing in the general population In sociological surveys the proportions of men and of women among those in various economic and age groups in various main parts of the country are often decided in advance. Then the investigator can set out knowing that he has to see, say 100 working-class London housewives, and can fairly quickly select women from houses in different streets in say a dozen different boroughs At the end of the process there is a reasonable chance of his having obtained a representative sample.

STAGE III —THE COLLECTION OF INFORMATION

The research being thoroughly planned the next stage is to collect the necessary data It is not always recognized that this is a task demanding as careful attention as do all the preceding and subsequent investigations Yet the most elaborately designed experiments, and the most refined statistical analysis, are worth no more than the original data and if these are faulty nothing can save the research.

We shall discuss three main topics first the use of figures and records already collected for their own ends by hospitals, government departments or other institutions secondly the design of forms and questionaries for recording information for a definite research and thirdly the principles of planning record sheets (such as individual case records) when the main purpose is a routine one and the possible research uses are not clearly known.

Before beginning this discussion it is opportune to emphasize the value to the statistician of complete individual information. The fullest and most satisfactory data are those relating to each individual case for though the techniques of statistics are able to deal with averages, rates, proportions, etc. applying to groups when the figures for each individual in the group are not provided, none the less the results are necessarily less certain and open to greater errors than when the full material is available.

Use of existing figures and records

The use of figures already collected demands the greatest caution, and the larger the organization which has collected them the more caution is needed It is essential in such cases to find out what the data really mean and how they have been obtained, rather than to accept the general descriptions in final returns and reports. The definitions used which determine what is actually being counted and how any given case is classified must be studied Often there may be

a difference in fundamental definition between two sets of figures which appear at first sight to relate to the same thing. Particularly in Government departments, figures tend to be collected by different branches for different purposes consequently there are considerable variations in scope and meaning. Thus the Personnel and Medical sides of a Service department will often have several sets of quite different figures of (for example) the numbers of wounded. Even in smaller institutions there may often be differences in diagnosis length of stay in hospital and so on, which must be carefully noted. It is equally important to know the channels through which figures have passed. Sometimes a multitude of sins lie hidden in some innocent looking consolidated table. In a certain department, known to the writer during World War II much confusion was caused by a very junior person who threw away all completed forms which looked to him improbable.

When information is to be specially obtained, the same sort of precautions must be observed, particularly when persons other than those who are familiar with the objects of the research have to record the data. Thus, only a few years ago, after all the materials had been collected, a large-scale research in a number of hospitals on the weight at birth and the subsequent growth of babies was entirely frustrated by a practice which was found to be usual in many of the hospitals. In order to lessen the mother s alarm at her baby's inevitable drop in weight in the first days of life, the nurses, unknown to their superiors, deducted a varying fraction of the total from the infants weight at birth.

Design of questionnaries and record sheets

Besides such difficulties there is the problem of designing record sheets or questionnaires so that they can be completed satisfactorily The aim must be to ensure that the information required is recorded with as little error as possible. Numerous errors arise from misunderstandings on the part of those questioned as to the real meanings of the questions, also from misunderstandings on the part of the investigators concerning the meanings of the answers, and finally from the difficulty of getting answers which are in the relevant form. For example, if a number of doctors have to record the duration of a hospital patient s illness, some will probably give the total stay in hospital, others a variety of different periods which conform to each doctor s idea of what is meant by duration of illness. An exact definition has to be provided, and the length of stay in hospital (except when another malady supervenes) will probably be the best period to choose, as it is, at least, not a matter of opinion. Here again, however one would have to say whether both, either or neither of the first and last days had to be counted. As an example of the second difficulty suppose, in a trial of several treatments, that there is a possibility of sulphonamide-sensitization occurring then, if the record sheet clearly asks whether or not it occurred, there can be no misunderstanding of what the doctor in charge of the case means. If however we merely ask for other relevant details some doctors may record all, or some, of the symptoms of sensitization without using the actual word sensitization and the investigator may be left in doubt whether or not to understand that sensitization occurred.

The third problem relates to getting a relevant answer The answers to such a question as Where do the lesions occur? may produce a variety of replies, some

giving very minute details others insufficient for the investigator's purpose If lesions occur in more than one place, some doctors may record all of the sites, others only the main or most important one Now the investigator is normally *the only person who knows what sort of answer he needs* Thus he may want to know whether chilblains, say were found on the hands, feet, nose and other sites. He may get answers ranging from half an inch from the top of the left little finger to upper part of the body The solution is as far as possible to use the method of restricted answers, in which the informant is provided with a list of alternative replies and asked to make a mark *against, or to underline, those which apply* To prevent the informant from feeling cramped a space may be left for comments in his own words. In this way an enormous amount of time and trouble can be saved, and more accurate information can be obtained. For example, suppose that one receives the reply Chilblains occur on the arms one can never be sure whether arms includes or excludes hands, whereas, if hands and arms are on a list and only arms are marked then one can be more sure how the word is being used

In general one can say that all record sheets as well as questionaries, essentially ask or should ask, questions. Therefore, in framing such forms it is necessary to ensure that all information is asked for absolutely clearly and unambiguously This seems at first sight to be simple enough but it is amazing how hard it is to ensure it in practice. In the case of questionaries designed to be answered by samples of patients or of other groups of individuals, the only way of *avoiding* misunderstandings is to test the questionary on small groups of people before it is used in earnest, so as to discover by actual experience, which questions have been well framed and which are unsatisfactory Another point to bear in mind and one which applies most to questionaries is that there are certain things which cannot be accurately ascertained by asking the individuals concerned *This is* due to defects of knowledge and to emotional resistances. Thus to ask the members of a sample of the population what diseases they or other members of their household had had during the previous month would *almost certainly be* extremely unreliable, except as an indication of the total amount of sickness. People tend not to know any but the vaguest details of their illnesses. *Further*more, if the investigator started to inquire about, say venereal disease, he would encounter emotional resistance which would probably prevent him from obtaining *any factual information In such a case the investigator would have to resort to* some indirect approach such as inquiries at venereal diseases clinics.

Design of record sheets

The preparation of questionaries involves much specialized experience and is not a task which it is generally advisable for those unused to them to undertake What has been said of them has been said mainly to illustrate the normally simpler record forms. The same sort of remarks apply to the design of case-record sheets *not intended* to form part of some particular research. *The golden rule here is to* decide in advance on certain points and always to set down the relevant information about them whatever else is recorded *It is a help if the chosen questions* can be printed on the sheet *More clinical data are wasted from neglect* of such precautions than from any other cause. If a clinician sometimes notes this factor and

sometimes that, his records are very probably useless as materials for scientific analysis, and they will, perhaps, amount to no more than a string of anecdotes about the most prominent features of his cases.

For scientific purposes, it is necessary to record information concerning the same factors in every case, and to keep to the set of factors chosen until a reasonable number of cases have been accumulated. It is almost as bad to keep adding to and modifying the type of information collected as not to collect any systematically This is not, of course, to say that all individual comments must be omitted, but merely that, in addition to what would be noted anyway certain definite questions should be answered. Science proceeds by observing uniformities, and a list of the odd things about 10 different cases of sensitization dermatitis, showing how one patient was sensitive to teak and another to alkaline solutions, is by itself of very little help

STAGE IV.—THE PRESENTATION OF DATA

We come now to the use of figures once they have been collected. It is not my purpose to say very much of the actual statistical method, as it is hoped that the non-statistical reader will, by now have a general and logical idea of what the statistician can do I shall devote myself to some of the simpler principles and methods of numerical presentation. This section has been called *The Presentation of Data* because essentially the statistician seeks to present his figures in such a way that the information inherent in them becomes manifest.

How the statistician will proceed to reduce to order the material collected will depend upon the nature of the research. Two of the main devices at his service are (1) the *average* and (2) the use of *ratios, percentages* and *proportions* The work of analysis has two stages first, the expression of the results in a form that enables their inherent properties to be clearly seen secondly the testing of the reliability of the differences observed, or other numerical conclusions, by estimating whether further experiments will or will not substantiate the results obtained.

The average: testing its significance

With regard to the first of the points of analysis if 2 treatments are each given to 50 men and the period of their stay in hospital is recorded, the 2 sets of 50 lengths of stay are not readily understandable in the raw Only when the 100 figures have been reduced to 2 averages, is it easy to see how the 2 treatments compare. As in this example, the first stage in analysing data is usually the isolation of a relevant difference or set of differences the second stage is to test the reliability of these differences. The range within which an average is expected to lie in further experiments is estimated from the dispersion around it of the individual observations. Obviously one has more confidence that an average will be within selected limits, the more concentrated are the observations around it. The wider they are scattered around it, the less precise become our justifiable inferences as to the true position of the average, and as to how likely it is that a difference between it and some other average is a real one. Provided that the observations are found to lie more or less symmetrically on either side of the mean, and to occur most frequently

close to it and become rarer as the distance from it increases, it is usually safe to take the range in which the true mean is likely to lie from the formula

$$\text{Experimental Mean plus or minus } 3\frac{S}{\sqrt{N-1}}$$

where N is the number of observations and S the standard deviation or square root of the average squared deviation from the mean Those interested in such formulae their uses and the assumptions on which they are based can consult a text book on statistics, such as Fisher s *Statistical Methods for Research Workers* or (perhaps easier to follow) Snedecor s *Statistical Methods* I am here concerned to point out that an average by itself is of very little use as one does not know between what limits the errors to which it is subject lie, and hence one cannot tell the significance of differences between it and other averages It is for this reason that it is important in collecting information to obtain the figures for each individual case, as it is by studying the internal consistency and range of variation between the individual cases that it is possible to estimate how much reliance should be placed on differences between averages, or on any other statistical coefficients which may be calculated If in trials of a drug, several hospitals report only average results much information is wasted and the results cannot be as closely assessed as if the full data had been obtained

Ratios and percentages

Ratios and percentages are also convenient devices for simplifying material. Ratios can be used to allow for the effect of some second variable or datum—as when sickness figures are converted into incidence rates, in order to remove the effects of changes in the size of the population concerned—or when complete information on a continuous variable is not or cannot be available. Thus, if we have instead of the complete data on the stay of cases in hospital only the numbers of patients who recovered within a given period under each of 2 treatments, we cannot calculate averages and the standard deviations, but have to work—rather less satisfactorily—with the 2 proportions.

Use of percentages —The use of percentages to simplify a table of figures is, of course, well known. They can sometimes give a misleading impression, how ever if substituted entirely for figures To say that under one method of treat ment 80 per cent of the patients recovered in a week while under a second the per centage to do so was only 40 sounds quite impressive, but if only 5 cases were treated by each method the results are not nearly so full of meaning as they sound In fact, particularly when the numbers involved are small the true figures on which the percentages are based should always be shown

The incidence ratio —The most familiar type of ratio in Medicine is the incidence ratio of a disease or condition obtained when the number of sufferers is divided by that of total relevant population and the result multiplied by 100 1 000 10 000 and so on, to give the percentage, rate per mille, etc. as incidence rates Thus if 120 cases of scabies are reported in a population of 12,000 during 1 month the monthly incidence of scabies is

$$\frac{120 \times 1\,000}{12,000} \text{ or } 10 \text{ per } 1\,000$$

It is not always realized that the ambiguity in the term, month, tends to obscure changes in incidence rates. Thus, if the word means calendar month a constant incidence of 1 per 1,000 per day would give an incidence for February of 28 per 1 000, and in March this would have risen to 31 per 1 000 or an increase of nearly 11 per cent. It is therefore advisable to adjust all rates to a constant period, such as a thirty-day month

Testing the significance of differences between ratios

To test the significance of a difference between 2 proportions or percentages, perhaps the simplest way is to use the original figures from which the ratios have been calculated. We can calculate how far each of the original figures deviates from what would have been expected on the assumption that the two percentages were really equal. Suppose that we are given a table showing the numbers and percentages of those persons, inoculated and not inoculated against some disease who subsequently caught that disease. We show the influence of inoculation upon susceptibility to subsequent infection by setting the table out in the form given in Table IV and calculating the numbers shown in brackets, which are those to be expected if inoculation made no difference to susceptibility to infection. If inoculation had no protective influence, then we should expect the proportion among the inoculated of those who subsequently caught the disease, to be the same as that among the uninoculated In other words, chance alone would decide into which of the 4 cells of the table, or categories (i.e. inoculated—subsequently infected inoculated—not infected not inoculated—subsequently infected not inoculated—not infected), a case would fall. On this basis the numbers shown in brackets, which are those expected in a cell, are obtained from the marginal totals, so that as the proportion infected is 160/400 and the number inoculated is 100, the expected number of inoculated individuals, subsequently infected is $100 \times 160/400 = 40$ and so on as in Table IV

TABLE IV INOCULATION AND SUSCEPTIBILITY TO SUBSEQUENT INFECTION

History	Inoculated	Not inoculated	Total
Subsequently infected	10 (40)	150 (120)	160
Not infected	90 (60)	150 (180)	240
Totals	100	300	400

The first figure represents the actual, the second (bracketed) figure the expected number of persons infected or not infected, respectively

In Table IV the difference between actual and expected numbers is 30 or 75 per cent short of expectation in the cell, inoculated—subsequently infected and the deviation of the table as a whole from expectation is highly significant statistically Such significance is tested by squaring in each cell the difference between actual and expected numbers and dividing by the expected numbers.

In such a table as this with only 4 categories, if the sum of the 4 quantities so calculated exceeds 7 the probability of the differences being due to chance is less than 1 100. This result is obtained by fairly elaborate mathematics, but tables giving the probabilities of various values of χ^2 (*chi squared*), the quantity calculated, for various circumstances, are given in books on statistics

Relations between two or more variables

The relation between 2 variables can often be detected by a graph or chart, or by the use of percentages and ratios The statistician using more elaborate methods is able approximately to express the relationship in mathematical form and to tell whether or not an observed relationship is likely to have arisen by chance He is also able to handle several variables at a time and to tell how far changes in 3 4 or more variables appear to affect a fifth variable. Such methods, for example, enable one to tell which of say 4 mental tests are best used to select men for a given job and how much importance to give to the results of each test. Alternatively he can show how far the percentages of unemployment, the latitude, the birth-rate, the population the amount spent by the local authority on health services, and the extent of overcrowding, influence infantile mortality Such methods could also be interestingly applied to problems of the analysis of the predisposing factors to certain diseases also to prognosis, since these are essentially questions involving multiple causation In such investigations the assistance of a statistician would of course be essential.

To return to the simpler type of question in which 2 variables only are concerned it is, perhaps, of interest to discuss what can be done without any special statistical knowledge as an example, consider the particular type of problem common in Medicine—that of demonstrating and allowing for the influence of age on a particular disease. If we have a complete analysis of all the cases of a disease and know the ages of everyone in the population concerned, we can calculate an incidence rate for each age and so solve the problem directly though the results would have to be tested for significance. Supposing, however that we have

TABLE V PRESENTATION OF INFLUENCE OF AGE UPON INCIDENCE

Age in years	Sample of Case of disease	Sample of Whole population	Relative susceptibility ratio	Relative percentage susceptibility
1–21	20 per cent	25 per cent	$\frac{4}{5}$	16 per cent
1–41	30 ,,	35 ,,	$\frac{6}{7}$	18 ,,
41–61	40 ,,	35 ,,	$1\frac{1}{7}$	24 ,,
60 and over	10 ,,	5 ,,	2	42 ,,
Totals – –	100 per cent	100 per cent	$[4\frac{4}{5}]$	100 per cent

only 2 samples the first showing the age distributions of the cases of the disease the other of the population concerned The sample of cases by itself would tell

as nothing. We need to use the percentage distribution by age-group of the sample of whole population as well. We might obtain a result such as is shown in Table V

The matter can be simply presented by setting the two age distributions side by side, but the full force of the relation is not brought out until the relative percentage susceptibility to the disease in each group is calculated. This tells us how 100 cases would be distributed if all the groups were equal in size—in other words, the relative chances that a member of any group has of catching the disease. These figures are obtained by dividing the figures in the first column of Table V by those in the second, and then converting the ratios obtained to a percentage basis in the ordinary way. Such ratios can be used for measuring how far changes in age composition of a population would be expected to affect the morbidity-rates of disorders. When, as is often the case, susceptibility to a disease has a distinct relationship with age we cannot immediately compare the crude rates of incidence in 2 populations with different age compositions, or in the same population at different dates, if time has altered its age composition. If however as well as these crude rates we have the 2 percentage-age distributions and the percentage-age incidence of the disease, we can allow for differences in age composition. Supposing that we wish to know how the incidence rate of the disease which we have discussed must be modified to make it comparable with that in a second population with the age distribution below we can proceed as in Table VI

TABLE VI. ADJUSTMENT FOR AGE DIFFERENCES BETWEEN TWO COMPARABLE POPULATIONS

Age in years	2nd population (age distribution)	Relative susceptibility ratios (from 1st population)	Product of (1) and (2)
1–20	15 per cent	$\frac{4}{5}$	12
21–40	28	$\frac{6}{7}$	24
41–60	42	$1\frac{1}{7}$	48
60 and over	15	2	30
			Total 114

1st population—population shown in Table V

Hence we have to increase the incidence in the first population by 114/100 to make it comparable with that in the second. Such a calculation assumes that the age incidence is the same in both populations. If it is not, then we must standardize both incidence rates by reference to a third arbitrary standard population in order to obtain the difference in incidence rates after allowing for the difference in age composition. The differences could be tested for significance by the use of χ^2 (*chi squared*) as described above.

I have dealt with this problem at some length because it would seem that individual hospitals could use such methods in presenting data which they could collect on their intake of patients. It would be possible to examine the age distributions of the different disorders and to relate them to the average distribution

of all incoming patients, and so on again the relation between age, incidence, and occupation could fruitfully be studied.

CONCLUSION

The writer hopes that this chapter has served not only to display the methods and uses of statistics but to convince readers how valuable some knowledge of the subject would be to members of the medical profession but to those who have not the time or inclination to take up the subject he would make two final recommendations First never embark on the collection of numerical data for research purposes (and still less publish the results) without consulting a statistician. Secondly never accept published results as proving anything unless all the quantitative conclusions are proved to have been tested for statistical significance.

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(See also Winner Albertine L. and Cooper Willis, E. S (1946). *Lancet* 2, 663 as an example of statistical method applied to an inquiry concerning Chilblains in Servicewomen)

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